IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Goldenberg

Serial No.: 10/002,211

Filed: December 5, 2001

Title: METHOD OF TREATING IMMUNE DISEASE USING B-CELL ANTIBODIES

Group Art Unit: 1644

Examiner: Chun Crowder

Attorney Docket No.: IMMU:003US1

EFS-WEB

DECLARATION UNDER 37 CFR §1.132

MAIL STOP AMENDMENT
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

Sir:

I, Kenneth Foon, being duly warned, declare as follows:

1. I am the Director of Clinical Investigation and Program Director for the Leukemia and Lymphoma Program at the University of Pittsburgh Cancer Institute Program and Professor of Medicine at the University of Pittsburgh School of Medicine. I have an extensive background in B cells and the field of immunotherapy for cancer treatment, as evidenced by my Curriculum Vitae, which is attached. In particular, I have been the principal investigator on clinical trials relating to immunotherapy of various B-cell malignancies with B-cell antibodies. I have known Dr. Goldenberg of Immunomedics and the Garden State Cancer Center for many years as a researcher in the field, and we interact at meetings. I also visited with him at the Garden State Cancer Center in New Jersey on several occasions about 5 or so years ago. I am being compensated on an hourly basis for my time in connection with this declaration.

2. I have read the Official Action dated July 26, 2007, for the above-captioned case. I have also reviewed the currently pending claims for this case and read the specification. I understand the examiner to question what one skilled in the relevant art circa 1992 would understand from reading the disclosure of this patent application. In particular, the examiner

seems concerned about whether one skilled in the art would understand that the inventor "had possession" of the invention of using B cell antibodies to treat immune diseases. In this regard, she seems to raise issues about whether the disclosure must include evidence of "relevant identifying characteristics" and/or "a disclosed correlation between function and structure" for B-cell antibodies in order to sufficiently describe the invention to a skilled artisan. She also says that the method depends upon "finding 'B-cell antibody'" and that "without such an antibody, the skilled artisan cannot practice the claims method of treating an immune disease." I also see that the examiner says that the claims call for B-cell antibodies or fragments generally and, in her words, "[lack] a common structure essential for the function (*e.g.* antigen specificity) and the claims do not require any particular structure basis or testable function be share by the instant 'B-cell antibody or fragment thereof.'" For the reasons which follow, I do not believe these concerns to be well-founded scientifically.

3. The Cluster of Differentiation (CD) is a protocol used for the identification and investigation of cell surface molecules present on leukocytes. CD molecules act in various ways, often acting as receptors or ligands (the molecule that activates a receptor) important to a cell. Binding to the CD antigen generally initiates a signal cascade that alters the behavior of the cell. The CD nomenclature was proposed and established at the 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA), which was held in 1982. The system was intended for the classification of the many monoclonal antibodies generated by different laboratories around the world against antigens/epitopes on the surface molecules of leukocytes. A proposed surface molecule is only assigned a CD number once two specific monoclonal antibodies are show to bind to the molecule. If a molecule has not been well characterized, or has only one monoclonal antibody, it is usually given the provisional indicator "w." I have attached a listing of the antigens from both the 4th and the 5th International Workshops. Since each CD represents at least two monoclonal antibodies, the attached lists show that there were many monoclonal antibodies to B cells that were known well before 1992.

4. One of the first B-cell antigens to be studied in depth was B1. In 1980, Stashenko *et al.* described and characterized a monoclonal antibody specific to this antigen. *J. Immunology*, 125(4)1678-1685 (1980), copy appended. The anti-B1 antibody was studied further and the following year this group reported that all tumor cells from patients with lymphomas or chronic lymphocytic leukemias, bearing either monoclonal K or light chain, express the Bl antigen. Nadler *et al.*, *J. Clin. Invest.* 67:134-140 (1981), abstract appended. In 1987, Liu *et al.* described a chimeric anti-CD20 antibody, 2H7, which recognized CD20 that is

expressed in normal as well as malignant B cells. *J Immunol.* 15(10):3521-6 (1987), abstract appended. Other scientists in the late 1980s and early 1990s were using B-cell antibodies to study the B-cell lineage of B-cell cancers, particularly (Non-Hodgkin's Lymphoma (NHL). For example, Schmid *et al.* and Shimoyama *et al.* were assessing the expression of B-cell antigens by B-cell malignancies (*Am. J. Pathology*, 139(4): 701-707 (1991) and *Japanese J. Clin. Oncol.* 13(3): 447-488 (1983), respectively, copy/abstract appended).

5. Not only were researchers describing anti-B-cell antibodies to characterize the B-cell lineage of B-cell malignancies, but in the late 1980s and early 1990s they also began to describe the use of B-cell antibodies for immunotherapy of B-cell malignancies. Press *et al.* used an anti-CD20 antibody, 1F5, to treat patients with refractory malignant B-cell lymphomas. *Blood*, 96(2):584-591 (1987), copy appended. While the effect was transient, the study showed that the binding of B-cell antibodies affected function of the targeted cells. This same group reported on the use of MB1, an anti-CD37 antibody, to successfully treat a small cohort of patients with NHL. Press *et al.*, *J Clin Oncol.* 7(8):1027-38 (1989), copy appended.

6. A large number of B-cell antibodies had already been developed by 1992, directed to different B-cell antigens. The genus of B-cell antibodies possesses a commonality of function. The function shared by members of the genus is the ability to bind to a B-cell antigen. I was the lead author on a paper published in 1987 entitled "Immunologic Classification of Leukemia and Lymphoma" (Foon and Todd, *Blood*, 68(1):1-31 (1987), copy appended). Table 1 of the article lists 30 monoclonal antibodies reactive with human B lymphocytes. Many of these were commercially available from companies such a Coulter Immunology and Ortho System, Inc. Thus, the disclosure of "B-cell antibodies" described to a person of skill in the art a large number of different antibodies, and not just the LL2 antibody that is mentioned in the above-captioned application. Many of these antibodies were freely available to those of skill in the art.

7. My aforementioned article also discloses that B-cell antibodies are useful in monoclonal antibody therapy of B-cell cancers. My article cites one study in which patients were treated with the BA-1, BA-2 and BA-3 monoclonal antibodies to B cells, and another in which patients were treated with anti-B1antibody. These studies both showed that the binding of B-cell antibodies to cancerous B cells affects disease progression. Thus, B-cell antibodies have been demonstrated to possess a commonality of function both in terms of their ability to specifically bind to B cells and also in the ability to affect disease progression as a result of that binding. In

the conclusion section of my paper I accurately predicted that B-cell antibodies would be found to be useful in the therapy of leukemias and lymphomas.

8. Patent applications for specific B-cell antibodies already were being filed in the late 1980s and early 1990s. For example, Robinson *et al.* filed an application in 1987 that was directed to the use of an anti-CD20 antibody in treating B-cell malignancies. This was published in 1988 as WO8804936 and gave rise to a number of US patents, including US5721108, US6204023, US6652852, US6893625 and others. These patents claim the 2H7 antibody that recognizes the BP35 anti-CD20 antigen. Ledbetter *et al.* filed an application in 1986 that disclosed the antibody G28-5. The antibody was used to define the B-cell receptor Bp50, and claims to the BP50 antigen issued in US 5,247,069. Each of these applicants deposited a hybridoma which secreted their claimed antibody.

9. The foregoing articles and patents establish that a large number of B-cell antibodies had been described and were commercially and/or publicly available prior to 1992. Therefore, a skilled artisan, reading the disclosure in the above-captioned case that:

- "ablation of certain normal organs and tissues for other therapeutic purposes, such as the spleen in patients with immune disease or lymphomas, the bone marrow in patients requiring bone marrow transplantation, or normal cell types involved in pathological processes, such as certain T-lymphocytes in particular immune diseases" (page 7, lines 5-10)

- Another therapeutic application for such organ- and tissue-targeting antibodies conjugated with a toxic agent is for the ablation of certain normal cells and tissues as part of another therapeutic strategy, such as in bone marrow ablation with antibodies against bone marrow cells of particular stages of development and differentiation, and in the cytotoxic ablation of the spleen in patients with lymphoma or certain immune diseases, such as immune thrombocytopenic purpura, etc. (page 9, lines 2-10)

- "Specific examples include antibodies and fragments against bone marrow cells, particularly hematopoietic progenitor cells, pancreatic islet cells, spleen cells, parathyroid cells, uterine endometrium, ovary cells,

testicular cells, thymus cells, B-cells, T-cells, Null cells, vascular endothelial cells, bile duct cells, gall bladder cells, prostate cells, hormone receptors such as of FSH, LH, TSH, growth factor receptors, such as of epidermal growth factor, urinary bladder cells, and vas deferens cells" (page 12, lines 12-20) and

- "Antibodies that target the spleen well include the LL2 (also known as EPB-2) monoclonal antibody, disclosed in Pawlak-Byczkowska, cancer Research, 49:4568-4577 (1989), which is directed against normal and malignant B cells, and which can be used for treating normal spleen cells in patients with immune diseases, lymphoma, and other diseases" (page 12, lines 30-35)

would understand that the applicant was in possession of a method of using B-cell antibodies generally to treat immune diseases, and not just the LL2 B-cell antibody specifically. The skilled artisan would understand that the contribution to the art was the teaching that B-cell antibodies generally could be used to treat immune diseases. These B-cell antibodies have a commonality of function, in that they all bind to B-cell surface antigens. In another context, that of B-cell cancers, this commonality of function has been found to correlate to an ability to affect disease progression as a result of that binding (I have discussed this in paragraph 7 above). This binding function is one that is testable, as I described in paragraph 3 above, and the skilled artisan would not need to know the structure of particular B-cell antibodies in order to be apprised of, and to practice, the full scope of this invention.

10. Also in the Official Action dated July 26, 2007, in the above-captioned case, I understand the examiner to say that the term "immune disease" would be unclear and ambiguous to a knowledgeable reader of the disclosure. As a hematologist, and in the context of the entire disclosure of the above-identified application, I do not find this term to be unclear or ambiguous. The term is used in conjunction with a discussion of the use of a B-cell antibody and also in conjunction with a disclosure of the ablation of normal spleen cells. The most common immune diseases then, and now, are autoimmune diseases. Accordingly, I understand the term "immune disease" in the application and the claims to mean autoimmune diseases.

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I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11/28/07

Date

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CURRICULUM VITAE

BIOGRAPHICAL

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EDUCATION AND TRAINING

UNDERGRADUATE:

Dates Attended	Name & Location of Institution	Degree Received and Year	Major Subject
1964-1966	University of Michigan		
1966-1968	Wayne State University	BS, 1968	Biology

GRADUATE:

Dates Attended	Name & Location of Institution	Degree Received and Year	Major Subject
1968-1972	Wayne State University	M.D, 1972	Medicine

POSTGRADUATE:

Dates Attended	Name & Location of Institution	Name of Program Director and Discipline
1972-1973	University of California, San Diego School of Medicine, San Diego, CA	Nathan Zvailler, MD Straight Internal Medicine Internship
1976-1977	Washington VA & Georgetown Hospitals, District of Columbia	Hyman Zimmerman, MD Straight Internal Medicine First Year Residency
1977-1980	University of California, Los Angeles Los Angeles, CA	Martin Cline, MD Fellow in Hematology and Oncology

ACADEMIC:

Years Inclusive	Name & Location of Institution	Rank/Title
1980-1981	University of California Los Angeles School of Medicine Los Angeles, CA	Assistant Professor of Medicine (tenure track)
1985-1987	University of Michigan School of Medicine Ann Arbor, MI	Associate Professor of Medicine (with tenure)
1985-1987	University of Michigan School of Medicine Ann Arbor, MI	Associate Chief, Div. of Hematology-Oncology Director of Clinical Hematology
1987-1991	State University of New York at Buffalo Buffalo, NY	Professor, Dept. of Medicine (with tenure)
1987-1991	Roswell Park Cancer Institute Buffalo, NY	Chief, Division of Clinical Immunology
1991-1992	Department of Molecular and Experimental Medicine, The Scripps Research Institute San Diego, CA	Adjunct Member

1991-1993	Ida M. and Cecil H.Green Cancer Center Scripps Clinic and Research Foundation San Diego, CA	Associate Director for Clinical Research
1993-1999	University of Kentucky School of Medicine Lexington, KY	Chief, Div. of Hematology-Oncology Professor of Medicine (with tenure)
1993-1999	Markey Cancer Center University of Kentucky School of Medicine Lexington, KY	Director
1999-2001	University of Cincinnati School of Medicine Cincinnati, OH	Associate Director Division of Hematology-Oncology Professor of Medicine (with tenure)
1999-2001	Barrett Cancer Center University of Cincinnati School of Medicine Cincinnati, OH	Director
2001-2003	Stanford University School of Medicine Stanford, CA	Clinical Professor of Medicine
2003-2006	University of Pittsburgh Cancer Institute	Co-Leader of the Biological Therapeutics Program
2005-Present	University of Pittsburgh Cancer Institute	Interim Director of Minority Outreach
2003-Present	University of Pittsburgh Cancer Institute	Director of Clinical Investigations Co-Leader of the Hematologic Malignancies Program
2003-Present	University of Pittsburgh School of Medicine	Professor of Medicine

NON-ACADEMIC

Years Inclusive	Name & Location of Institution	Rank/Title
1973-1975	National Eye Institute, National Institutes of Health Bethesda, MD and guest worker National Institute of Dental Research, Laboratory of Microbiology and Immunology Bethesda, MD	Research Associate and Lieutenant, U.S. Public Health Service
1975-1976	National Institute of Dental Research, Laboratory of Microbiology and Immunology, National Institute of Health, Bethesda, MD	Clincial Associate and Lieutenant Commander, U.S. Public Health Service
1981-1982	Head, Monoclonal Antibody-Hybridoma Section, Biological Response Modifiers Program, Division of Cancer Treatment, National Cancer Institute Frederick, MD	Senior Investigator and Lieutenant Commander, U.S. Public Health Service
1982-1985	Head, Clinical Investigations Section, Biologic Response Modifiers Program, Division of Cancer Treatment National Cancer Institute Frederick, MD	Senior Investigator and Lieutenant Commander, U.S. Public Health Service (tenured in 1984)
2001-2003	Abgenix Inc. Fremont, CA	Director, Clinical Development for Oncology

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CERTIFICATION AND LICENSURE

Specialty Certification:

Certifying Board	Year

National Board of Medical Examiners	1973
American Board of Internal Medicine	1978
American Board of Internal Medicine Subspecialty of Hematology	1980
American Board of Internal Medicine Subspecialty of Medical Oncology	1981

Medical Licensure:

Licensing Board/State	**Year**
California (active)	1973
Maryland (inactive)	1973
Virginia (inactive)	1973
District of Columbia (inactive)	1973
Michigan (inactive)	1982
New York (inactive)	1987
Kentucky (inactive)	1993
Ohio (inactive)	1999
Pennsylvania (Active)	2003

MEMBERSHIPS IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

Organization	**Year**
American College of Physicians (Fellow)	1978-present
American Society of Hematology	1980-present
American Association for the Advancement of Sciences	1980-present
American Society of Clinical Oncology	1981-present

American Association for Cancer Research	1982-present
The International Society of Biological Therapy	1982-present
Clinical Immunology Society	1987-present
Member, Leukemia Committee, Southwest Oncology Group	1987-2001
International Society for Experimental Hematology	1991-1996
Member, Colorectal Disease Committee, National Surgical Adjuvant Breast and Bowel Project	1997-2001
Member, Melanoma Committee, Southwest Oncology Group	1997-2000
Member, Colorectal Committee, American College of Surgeons Oncology Group	1999-2001
Member, Lymphoma, Committee, Eastern Cooperative Oncology Group (ECOG)	2003-Present
Member, Leukemia Committee, ECOG	2003-Present

HONORS

Title of Award	**Year**
Alpha Omega Alpha	1971
Dr. A. Ashley Rousuck Award in Internal Medicine (Wayne State University School of Medicine)	1971
Gordon B. Myers Award in Internal Medicine (Wayne State University School of Medicine)	1972
Medical Degree Awarded with High Distinction, Wayne State University	1972

Fellow of the American College of Physicians	1982
Distinguished Alumni Award, Wayne State University School of Medicine	1987
Michigan Science Trailblazer	1988
Faculty Research Award for Excellence in Research, University of Kentucky	1998
Chairman's Award for Excellence in Research, University of Kentucky, Dept. of Internal Medicine	1998

PUBLICATIONS

1. Refereed Articles

1. **Foon KA**, Wahl SM, Oppenheim JJ and Rosenstreich DL: Serotonin-induced production of a monocyte chemotactic factor by human peripheral blood leukocytes. J Immunol 117:154-1552, 1976.

2. Sher NA, **Foon KA**, Fishman ML and Brown T: Demonstration of monocyte chemotactic factors in the aqueous humor during experimental immunogenic uveitis in the rabbit. Infect Immun 13:1110-1116, 1976.

3. Sher ND, Douglas DJ, Mindrup E, Minaii LA and **Foon KA**: Macrophage migration inhibition factor activity in the aqueous humor during experimental corneal xenograft and allograft rejection. Am J Ophthalmol 82:858-865, 1976.

4. **Foon KA**, Yuen K, Ballintine E and Rosenstreich D: Analysis of the systemic corticosteroid sensitivity of patients with primary open angle glaucoma. Am J Ophthalmol 83:167-173, 1977.

5. **Foon KA**, Naiem F, Yale C and Gale RP: Acute myelogenous leukemia: Morphologic subclass and response to therapy. Leuk Res 3:171-173, 1979.

6. **Foon KA**, Billing RJ and Terasaki PI: Dual B and T markers in acute and chronic lymphocytic leukemia. Blood 55:16-20, 1980.

7. Billing RJ, Clark BM, Koeffler P, **Foon KA** and Terasaki PI: Acute myelocytic leukemia heteroantisera. Clin Immunol Immunopathol 16:202-210, 1980.

8. **Foon KA**, Yale C, Clodfelter K and Gale RP: Effect of posttreatment hepatitis on survival of patients with acute myelogenous leukemia. JAMA, 244:1806-1807, 1980.

9. **Foon KA**, Fitchen JH, Billing RJ, Belzer MB, Terasaki PI and Cline MJ: An antithymocyte serum non-cytotoxic to myeloid progenitor cells: Candidate serum for prevention of graft-versus-host disease in bone marrow transplantation. Clin Immunol Immunopathol 16:416-422, 1980.

10. **Foon KA**, Billing RJ, Terasaki PI and Cline MJ: Immunologic classification of acute lymphocytic leukemia: Implications for normal lymphoid differentiation. Blood 56:1120-1126, 1980.

11. **Foon KA**, Herzog P, Billing R, Terasaki PI and Feig S: Immunologic classification of childhood acute lymphocytic leukemia. Cancer 47:280-284, 1981.

12. **Foon KA**, Naeim F, Saxon A, Stevens R and Gale RP: Leukemia of T-helper lymphocytes: Clinical and functional characterization. Leuk Res 5:1-10, 1981.

13. **Foon KA**, Billing RJ, Fitchen JH, Belzer MB, Drew SI and Terasaki PI: An antigen expressed by cells of the myelo-monocytic lineage. Am J Hematol 10:259-267, 1981.

14. Belzer M, Fitchen JH, Ferrone S, **Foon KA**, Billing RJ and Golde DW: Expression of HLA-DR antigen on human erythroid progenitor cells as determined by monoclonal anti-DR antibodies and heteroantiserum. Clin Immunol Immunopathol 20:111-115, 1981.

15. Gale RP, **Foon KA**, Cline MJ and Zighelboim J: Intensive chemotherapy for acute myelogenous leukemia. Ann Intern Med 94:753-757, 1981.

16. Fitchen JH, **Foon KA** and Cline MJ: The antigenic characteristics of hematopoietic stem cells. N Engl J Med 305:17-25, 1981.

17. **Foon KA**, Zighelboim J, Yale C and Gale RP: Intensive chemotherapy is the treatment of choice for elderly patients with acute myelogenous leukemia. Blood 58:467-470, 1981.

18. **Foon KA**, Filderman A and Gale RP: Histiocytic lymphoma following resolution of sarcoidosis. Med Pediatr Oncol 9:325-331, 1981.

19. Hoffman F, **Foon KA**, Smith D, Kransler J, Ciciarelli J and Billing R: Functional properties of subsets of T lymphocytes defined by special antigens. Clin Exp Immunol 44:476-484, 1981.

20. Hocking WG, Billing R.J, **Foon KA** and Golde DW: Human alveolar macrophages express DR antigens. Blood 58:1040-1042, 1981.

21. Linker-Israeli M, Billing RJ, **Foon KA** and Terasaki PI: Monoclonal antibodies reactive with acute myelogenous leukemia cells. J Immunol 127:2473-2477, 1981.

22. Billing R, Terasaki PI, Sugich L and **Foon KA**: Detection of differentiation antigens by use of monoclonal antibodies. J Immunol Methods 47:289-294, 1981.

23. Schroff RW, **Foon KA**, Billing RJ and Fahey JL: Immunologic classification of lymphocytic leukemias based on monoclonal antibody-defined cell surface antigens. Blood 59:207-215, 1982.

24. **Foon KA** and Haskell CM: Inadvertent overdose with lomustine (CCNU) followed by hematologic recovery. Cancer Treat Reports 66:1241-1241, 1982.

25. **Foon KA** and Gale RP: Controversies in the therapy of acute myelogenous leukemia. Am J Med 72:963-979, 1982.

26. **Foon KA**, Schroff RW and Gale RP: Cell surface markers on leukemia and lymphoma cells: Recent advances. Blood 60:1-19, 1982.

27. Billing RJ, **Foon KA** and Linker-Israeli M: The immunological classification of leukemia based on a rapid microcytoxicity test. Clin Exp Immunol 49:142-148, 1982.

28. Schroff RW and **Foon KA**: Heterogeneity in a lymphoid tumor: Co-expression of T and B surface markers. Blood 60:373-380, 1982.

29. **Foon KA**, Schroff RW and Fliegel S: Monoclonal antibody characterization of plasmacytoma cells associated with T lymphocytes with a suppressor phenotype. Clin Immunol Immunopathol 25:59-66, 1982.

30. **Foon KA**, Bernhard MI and Oldham RK: Monoclonal antibody therapy: Assessment by animal tumor models. J Biol Response Mod 1:277-304, 1982.

31. Sherwin SA, Knost JA, Fein S, Abrams PG, **Foon KA**, Ochs JJ, Schoenberger C, Maluish AE and Oldham RK: A multiple dose phase I trial of recombinant leukocyte A interferon in cancer patients. JAMA 248:2461-2466, 1982.

32. Key ME, Bernhard MI, Hoyer LC, **Foon KA**, Oldham RK and Hanna MG: Guinea pig line 10 hepatocarcinoma model for monoclonal antibody serotherapy: *In vivo* localization of a monoclonal antibody in normal and malignant tissues. J Immunol 120:1451-1457, 1983.

33. Sherwin SA, Mayer D, Ochs JJ, Abrams PG, Knost JA, **Foon KA**, Fein S and Oldham RK: Recombinant leukocyte A interferon in advanced breast cancer: Results of a Phase II efficacy trial. Ann Intern Med 98:598-602 1983.

34. Bernhard MI, **Foon KA**, Oeltmann TN, Key ME, Hwang KM, Clarke CG, Christensen WL, Hoyer LC, Hanna MG and Oldham RK: Guinea pig line 10 hepatocarcinoma model: Characterization of monoclonal antibody and *in vivo* effect of unconjugated antibody and antibody conjugated to diptheria toxin A chain. Cancer Res 43:4420-4428, 1983.

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36. **Foon KA**, Smalley RV, Riggs CW and Gale RP: The role of immunotherapy in acute myelogenous leukemia. Arch Intern Med 143:1726-1734, 1983.

37. Knost JA, Sherwin SA, Abrams PG, Ochs JJ, **Foon KA**, Williams R, Tuttle R and Oldham RK: The treatment of cancer patients with human lymphoblastoid interferon: A comparison of two routes of administration. Cancer Immunol Immunother 15:148-155, 1983.

38. Abrams PG, Knost JA, Clarke G, Wilburn S, Oldham RK and **Foon KA**: Determination of the optimal human cell lines for development of human hybridomas. J Immunol 131:1201-1204, 1983.

39. **Foon KA**, Buescher S, Kimball ES, Huang LC, Stevenson HC, Clarke G, Gregoria T and Harley JB: Monoclonal antibody to human eosinophils recognizing 95 kD surface membrane antigen. Hybridoma 2:393-402, 1983.

40. Stevenson HC, **Foon KA**, Kanapa DJ, Favilla T, Beman J and Oldham RK: The potential value of cytapheresis for adoptive immunotherapy of cancer patients. Plasma Ther Transfus Technol 5:237-250, 1984.

41. Hwang JM, **Foon KA**, Cheung PH, Pearson JW and Oldham RK: Selective antitumor effect on L10 hepatocarcinoma cells of a potent immunoconjugate composed of the A chain of abrin and a monoclonal antibody to a hepatoma-associated antigen. Cancer Res 44:4578-4586, 1984.

42. **Foon KA**, Mutsuyasu RT, Schroff RW, McIntyre RE, Champlin R and Gale RP: Immune deficiency in young males with hepatitis-associated severe aplastic anemia. Ann Intern Med 100:657-662, 1984.

43 Oldham RK, Morgan AC, Woodhouse CS, Schroff RW, Abrams PG and **Foon KA**: Monoclonal antibodies in the treatment of cancer: Preliminary observations and future prospects. Med Oncol Tumor Pharmacother 1:51-62, 1984.

44. Abrams PG, Ochs JJ, Giardina SL, Morgan AC, Wilburn SB, Wilt AR, Oldham RK and **Foon KA**: Production of large quantities of human immunoglobulin in the ascites of athymic mice: Implication for the development of anti-human idiotype monoclonal antibodies. J Immunol 132:1611-1613, 1984.

45. Stevenson HC, Ochs JJ, Halverson L, Oldham RK, Sherwin SA and **Foon KA**: Recombinant alpha interferon in retreatment of two patients with pulmonary lymphoma. Dramatic responses with resolution of pulmonary complications. Am J Med 77:355-358, 1984.

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47. Champlin R, Jacobs A, Gale RP, Boccia R, Elashoff R, **Foon KA** and Zighelboim J: Prolonged survival in acute myelogenous leukemia without maintenance chemotherapy. Lancet 1:894-896, 1984.

48. Schroff RW, Farrell MM, Klein RA, Oldham RK and **Foon KA**: T65 antigen modulation in a phase I monoclonal antibody trial with chronic lymphocytic leukemia patients. J Immunol 133:1641-1648, 1984.

49. **Foon KA**, Neubauer RH, Wikstrand CJ, Schroff RW, Rabin H and Seeger RC: Human Thy-1 antigen: Distribution on human and non-human primate hematopoietic cells. J Immunogenet 11:233-244, 1984.

50. **Foon KA**, Schroff RW, Bunn RA, Mayer D, Abrams PG, Fer MF, Ochs JJ, Bottino GC, Sherwin SA, Herberman RB and Oldham RK: Effects of monoclonal antibody therapy in patients with chronic lymphocytic leukemia. Blood 64:1085-1094, 1984.

51. Oldham RK, **Foon KA**, Morgan AC, Woodhouse C, Schroff RW, Abrams PG, Fer MF, Schoenberger C, Farrell M, Kimball E and Sherwin SA: Monoclonal antibody therapy of malignant melanoma: *In vivo* localization in cutaneous metastasis after intravenous administration. J Clin Oncol 2:1235-1244, 1984.

52. Reynolds CW and **Foon KA**: T-lymphoproliferative disease and related disorders in man and experimental animals. A review of the clinical, cellular and functional characteristics. Blood 64:1146-1158, 1984.

53. Fer MF, Bottino GC, Sherwin SA, Hainesworth JD, Abrams PG, **Foon KA** and Oldham, RK: Atypical tumor lysis syndrome in a patient with T-cell lymphoma following recombinant interferon therapy. Am J Med 77:953-956, 1984.

54. Bunn PA, **Foon KA**, Idhe DC, Winkler CF, Zeffren J, Sherwin SA and Oldham RK: Recombinant leukocyte A interferon: An active agent in advanced cutaneous T-cell lymphoma. Ann Intern Med 101:484-487, 1984.

55. Stevenson HC, Kimball ES, Buescher S, Clarke G and **Foon KA**: Monoclonal antibody to human monocytes and granulocytes: Isolation of membrane antigens and lack of effect on leukocyte functions *in vitro*. Hybridoma 3:247-261, 1984.

56. **Foon KA**, Sherwin SA, Abrams PG, Longo DL, Fer MF, Stevenson HC, Ochs JJ, Bottino GC, Schoenberger CS, Zeffren J, Jaffe ES and Oldham RK: Treatment of advanced non-Hodgkin's lymphoma with recombinant leukocyte A interferon. N Engl J Med 311:1148-1152, 1984.

57. Morgan AC, Woodhouse CS, Knost JA, Abrams PG, Clarke GC, Arthur LO, McIntrye R, Ochs JJ, **Foon KA**, Hanna MG and Oldham RK: Monoclonal antibodies to human colorectal tumor-associated antigens: Improved elicitation and subclass restriction. Hybridoma 3:233-245, 1984.

58. Sherwin SA, **Foon KA**, Oldham RK, Abrams PG, Heyman MR, Ochs JJ, Watson R and Maluish A: A preliminary phase I trial of partially purified interferon-gamma (IFN-gamma) in patients with disseminated cancer. Biol Response Mod 3:599-607, 1984.

59. Bunn PA, Carrasquillo JA, Keenan AM, Schroff RW, **Foon KA**, Hsu SM, Gazdar AF, Reynolds JJ, Perentesis P and Larson SM: Imaging of T-cell lymphoma by radiolabeled monoclonal antibody. Lancet 1219-1221, 1984.

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4. Other Publications

1. **Foon KA** and Gale RP: Post-transfusion hepatitis in acute myelogenous leukemia. JAMA 246:216, 1981 (letter)

2. **Foon KA**, Zighelboim J and Gale RP: Treatment of acute myelogenous leukemia in older patients. N Engl J Med 305:1470, 1981. (letter)

3. **Foon KA**: Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med 307:686, 1982. (letter)

4. Bernhard MI, **Foon KA**, Oldham RK and Keenan A: The importance of traditional methods of measuring tracer biodistributions. Cancer Res 44:2731-2732, 1984. (letter)

5. **Foon KA** and Dougher G: Increased growth of eyelashes in a patient given leukocyte A interferon. N Engl J Med 311:1259, 1984. (letter)

6. **Foon KA** and Schroff RW: The uses of monoclonal antibodies in the diagnosis and treatment of leukemia and lymphoma. In: *In Vitro Monograpy*, No. 5. 1984, pp 169-188.

7. Abrams PG, McClamrock EA and **Foon KA**: Evening administration of alpha interferon. N Engl J Med 312:443-444, 1985. (letter)

8. Reynolds CW, **Foon KA** and Herberman RB: Terminology in Tγ lymphoprolifertive disease. Blood 66:248-249, 1985. (letter)

9. **Foon KA**: Interferon-alpha: The next decade. Interactions 1:3, 1986. (editorial)

10. **Foon KA:** Interferons. Hoffman La Roche, 1986. (video)

11. **Foon KA**: Biological therapy of chronic myelogenous leukemia. Oncology 1:49-52 1987. (editorial)

12. **Foon KA**: Application of monoclonal antibodies in the diagnosis and therapy of cancer. NeoRx Pharm Inc, 1988, pp 1-27. (monograph)

13. **Foon KA:** Antibody Structure and Function. NeoRx Pharm Inc, 1988. (video).

14. **Foon KA:** Therapy of Acute Leukemia: Recent Progress and Future Directions. Wyeth Labortories, 1988. (video)

15. **Foon KA**, Champlin RE and Gale RE: Therapy of acute lymphoblastic leukemia. UCLA Symposium. In: *Acute Lymphoblastic Leukemia*, Vol. 108., pp 157-196, 1990.

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18. **Foon KA:** Cancer Vaccine Therapy: New Approaches, Video Journal of Oncology, Secaucus, NJ 1993. (video)

19. **Foon KA** and Bhattacharya-Chatterjee M. Idiotype vaccines in the clinic. Nature Med 4:870, 1998. (letter)

20. **Foon KA**: Translational Research: Advancing Medical Science by Stimulating Interdisciplinary Research. Exp Biol Med (Maywood). 2007 Jun; 232(6):713-4. (editorial)

TEACHING

Biotherapy: New Opportunities for Cancer Treatment, Grand Rounds, Scripps Clinic and Research Foundation, La Jolla, CA, February 28, 1992.

Acute Leukemia, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, August 16, 1993.

Hodgkin's Disease, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, September 10, 1993.

Biologic Therapy and Growth Factors, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, October 8, 1993.
Anti-Idiotype Immunotherapy in Cancer Patients, Lecture-Division of Clinical Chemistry, University of Kentucky Hospital, Lexington, KY, April 27, 1994.

Chronic Lymphocytic Leukemia, Internal Medicine Grand Rounds, University of Kentucky Medical Center, Lexington, KY, July 6, 1994.

Acute Leukemia, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, August 16, 1994.

Anti-Idiotype Vaccine Therapy of CEA positive tumors, Internal Medicine Research Seminar, University of Kentucky Medical Center, Lexington, KY, September 8, 1994.

Melanoma, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, February 3, 1995.

Lymphoma, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, March 23, 1995.

Chronic Lymphocytic Leukemia, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, April 28, 1995.

Overview of the Cancer Center, Health Administration, University of Kentucky Medical Center, June 22, 1995.

Non-Hodgkin's Lymphoma, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, September 11, 1995.

Hodgkin's Disease, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, September 15, 1995.

Non-Hodgkin's Lymphoma, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, September 29, 1995.

Chronic Lymphoid Leukemias, Hematology-oncology grand Rounds, Confernce, Univeristy of Cincinnati, Cincinnati, OH, September 28, 2000

Colon Cancer, Internal Medicine residency Program, University of Cincinnati, Cincinnati, OH, September 27, 2000

Non-Hodgkin's Lymphoma, Internal Medicine residency Program, University of Cincinnati, Cincinnati, OH, June 26, 2000

Melanoma, Internal Medicine Residency Program, University of Cincinnati, Cincinnati, OH, April 14, 2000.

Lymphoma, Internal Medicine Residency Program, University of Cincinnati, Cincinnati, OH, March 13, 2000.

Anti-Idiotype Cancer Vaccines, Children's Hospital Medical Center Research Foundation, Basic Sciences, Cincinnati, OH, January 31, 2000.

Cancer Research, Division of Pharmacology, Ph.D. Program, University of Cincinnati, OH, January 7, 2000.

Lymphomas, Internal Medicine Residency Program, University of Cincinnati, Cincinnati, OH, January 6, 2000.

Melanoma, Internal Medicine Residents, University of Cincinnati Hospital, June 24, 1999.

Anti-Idiotype Cancer Vaccines, Children's Hospital Medical Center Research Foundation, Basic Scientists, January 31, 2000.

Cancer Research, Division of Pharmacology, Ph.D. Program, University of Cincinnati College of Medicine, January, 7, 2000.

Lymphomas, Internal Medicine Residents, University of Cincinnati Hospital, January 6, 2000

Melanoma, Internal Medicine Residents, Univeristy of Cincinnati Hospital, Cincinnati, OH, December 9, 1999.

Lymphomas, Internal Medicine Residents, University of Cincinnati Hospital, October 4, 1999.

Lymphomas, Internal Medicine Residents, University of Cincinnati Hospital, September 14, 1999.

A Novel Immunotherapeutic Approach for the Adjuvant Treatment of Colon Cancer, Internal Medicine Grand Rounds, University of Kentucky Medical Center, Lexington, KY, September 4, 1996.

Melanoma, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, August 16, 1996.

Acute Leukemia, Internal Medicine Residency Program, University of Kentucky Medical Center, Lexington, KY, August 8, 1996.

Low Grade Lymphomas, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, June 28, 1996.

Problem Based Learning Tutor Session, Internal Medicine, University of Kentucky Medical Center, April 1-15, 1996.

Leukemia and Lymphoma, Physician Assistants Lecture, University of Kentucky Medical Center, March 7, 1996.

Acute Leukemias, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, February 2, 1996.

Non-Hodgkin's Lymphoma, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, September 29, 1995.

Hodgkin's Disease, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, September 15, 1995.

Low Grade Lymphomas, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, June 28, 1996.

Problem Based Learning Tutor Session, Internal Medicine, University of Kentucky Medical Center, April 1-15, 1996.

Leukemia and Lymphoma, Physician Assistants Lecture, University of Kentucky Medical Center, March 7, 1996.

Acute Leukemias, Hematology/Oncology Fellows Board Review Lecture Series, University of Kentucky Medical Center, February 2, 1996.

Grand Rounds, University of Cincinnati Hospital, Cincinnati, OH, 2004.

Medical Grand Rounds, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, 2004

Presentations for Lymphoma/Leukemia Tumor Board, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, 2003-2006.

Presentations for Hematologic Malignancies Program Seminar Series, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, 2003-2006.

Presentations for Biologic Therapeutics Committee, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, 2003-2006.

Presentations for Hematologic Malignancy Steering Committee, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, 2003-2006.

Nipent® (pentostatin) in CLL, Supergen Nipent® Strategic Planning Community Advisory Board, Detroit, Michigan, August 6, 2005.

Recent Advances in the Biology and Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Supergen, January 14, 2005

Leukemia and Lymphoma, Houseteaching Staff Lecture Series for Residents, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, July 17, 2003; October 24, 2003; and November 7, 2003.

Leukemia and Lymphoma, Houseteaching Staff Lecture Series for Residents, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, February 24, 2004; April 1, 2004; May 10, 2004, and June 22, 2004.

Leukemia and Lymphoma, Houseteaching Staff Lecture Series for Residents, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology, January 14, 2005; February 15, 2005; March 29, 2005; May 23, 2005; July 21, 2005.

Monoclonal Antibodies and The Paradigm Shift in the Treatment of B-Cell Lymphomas and Leukemias, Hematology/Oncology Fellows Lecture Series, University of Pittsburgh School of Medicine/Department of Hematology/Oncology, June 17, 2005.

Recent Advances in the Biology and Treatment of Low Grade Lymphomas, Lecture Series for Hematology/Oncology Fellows, University of Pittsburgh School of Medicine, Department of Medicine, Division of Hematology/Oncology; May 5, 2006.

Leukemia and Lymphoma, Houseteaching Staff Lecture Series for Residents, University of Pittsburgh School of Medicine/Department of Hematology/Oncology, March 2, 2006; May 1, 2006; June 8, 2006; July 18, 2006.

Recent Advances in the Biology and Treatment of Low Grade Lymphomas "Overview of Lymphoma" as part of Neoplasia Course; Facilitator for Case 4 "Erythocytosis" of PBL cases; January 2005.

"Recent Advances and Clinical Aspects in the Treatment of CLL," sponsored by Georgia Cancer Foundation, Atlanta, GA, March 23, 2006

Current Therapeutic Modalities in the Management of CLL, Cleveland, OH, April 20, 2006.

Mentored Jennifer Larson, 4th year Medical student, and assisted w/her poster presentation, summer 2005.

Mentored Christopher Marsh, MD, resident, and assisted him w/his presentation, spring 2006.

Recent Advances and Clinical Aspects in the Treatment of CLL/SLL, Hematology/Oncology Fellows CME Lecture, University of Pittsburgh School of Medicine/Department of Hematology/Oncology, Sponsored by Berlex Pharmaceuticals, Soba Restaurant, Shadyside, Pittsburgh, PA, September 12, 2006.

Recent Advances and Clinical Aspects in the Treatment of CLL/SLL, Oncology Grand Rounds, USC Keck School of Medicine, Los Angeles, California, sponsored by CBCE Speakers Corp., September 22, 2006.

Clinical Care of Lymphoproliferative Disorders, Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, part of Hematology Course for 4th year Medical School Students, January 11, 2007.

Current therapeutic Modalities in the Management of CLL, Valley View, OH, CME course sponsored by Cogenix supported by a grant from Berlex, Inc., April 20, 2006.

Eliminating MRD: A Realistic Response Criterion in CLL Management, Soba Restaurant, Pittsburgh, PA, CME course sponsored by the Institute for Advanced Health Education supported by a grant from Berlex, Inc., September 12, 2006.

Rituxan® (Rituximab) Therapy for the Treatment of Relapsed or Refractory, Low-Grade or Follicular, CD20+, B-Cell Non-Hodgkin Lymphoma, Morton's of Chicago-Pittsburgh, Pittsburgh, PA, CME course sponsored by Genentech Integrated Education, September 28, 2006.

Rituxan® (Rituximab) Therapy for the Treatment of Relapsed or Refractory Low-Grade or Follicular, CD20+, B-Cell Non-Hodgkin Lymphoma, Altoona Hospital, Altoona, PA, CME course sponsored by Genentech Integrated Education, October 10, 2006.

Rituxan® (Rituximab) therapy for the Treatment of Relapsed or Refractory Low-Grade or Follicular, CD20+, B-Cell Non-Hodgkin Lymphoma, Morton's of Chicago-Pittsburgh, Pittsburgh, PA, CME course sponsored by Genentech Integrated Education, October 17, 2006.

Recent Advances in the Biology and Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Hematology/Oncology Grand Rounds, Good Samaritan Medical Center, West Palm Beach, FL, CME course sponsored by EXCEL Continuing Education, October 19, 2006.

Rituxan® (Rituximab) Therapy for the First-line Treatment of Diffuse Large B-Cell, CD20+, Non-Hodgkin Lymphoma in Combination with CHOP or Other Anthracycline-Based Chemotherapy Regimens, Morton's of Chicago-Pittsburgh, Pittsburgh, PA, sponsored by Genentech Integrated Education, October 24, 2006.

Recent Advances in the Biology and Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, 2nd Annual Meeting of the Association of VA Hematology/Oncology, Kingsgate Marriott Conference Hotel at University of Cincinnati, Cincinnati, OH, sponsored by AVAHO, November 2, 2006.

Interdisciplinary Care for Patients with Mycosis Fungoides (Dermatology, Hematology/Oncology/Blood Bank, Radiation Therapy, Pathology, Experimental Therapeutics/Immunology), part of the Cutaneous Lymphoma, Regional Masters Conference, CME course sponsored by Ligand, November 2, 2006.

Current Therapeutic Modalities in the Management of CLL, Eleven, Pittsburgh, PA, CME course sponsored by Cogenix supported by a grant from Berlex, Inc., November 20, 2006.

Rituxan® (Rituximab) Therapy for the Front-line Treatment of Low-Grade or Follicular, CD20+, B-Cell Non-Hodgkin Lymphoma, Eleven, Pittsburgh, PA, CME course sponsored by Genentech Integrated Education, November 28, 2006.

Rituxan® (Rituximab) Therapy for the First-line Treatment of Diffuse Large B-Cell, CD20+, Non-Hodgkin Lymphoma in Combination with CHOP or Other Anthracycline-Based Chemotheapy Regimens, Monterey Bay Fish Grotto, Monroeville, PA, CME course sponsored by Genentech Integrated Education, December 4, 2006.

Precursor B- and T-Cell Lymphoblastic Lymphoma, Chief of Medicine Conference Presentation, University of Pittsburgh School of Medicine, Pittsburgh, PA, December 14, 2006.

Chronic Lymphocytic Leukemia: Recent Advances in Biology and Therapy, Department of Internal Medicine Grand Rounds, University of Missouri – Columbia, Columbia, MO, March 22, 2007.

Recent Advances in the Biology and Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Seminar, Stanley S. Scott Cancer Center, LSU Health Sciences Center, New Orleans, LA, April 2, 2007.

Rituxan® (Rituximab) Therapy for the Front-line Treatment of Low-grade or Follicular, CD20+, Non-Hodgkin Lymphoma, Morton's of Chicago – Pittsburgh, Pittsburgh, PA, May 3, 2007.

Rituxan® (Rituximab) Therapy for the Front-line Treatment of Low-grade or Follicular, CD20+, B-Cell Non-Hodgkin's Lymphoma, Malone's Banquets, Lexington, KY, July 19, 2007.

RESEARCH:

1. Current Grant Support:

Grant Number (Funded)	Grant Title	Role in Project & Effort (in cal. Mths.)		Years Inclusive	Source $ Amount
NIH PO1-CA109688	Immune Escape in Human Cancer: Mechanisms and Therapeutic Implications	Co-investigator	3.0	11/01/06-10/31/11	$1,071,960 (annual direct)
NIH RO1 CA72018	Ganglioside GD2 as Target for Immunotherapy in Melanoma	PI	3.0	8/01/05-8/30/09	$1,250, 000 (total direct)
Metanexus Institute on Religion and Science	Take Five – For You: Clinical study to evaluate mental and emotional support for patients with newly diagnosed acute leukemia	Co-PI	2.0	6/1/06-5/30/09	$929,960 (total direct)
C-Change	A Statewide Cancer Clinical Trials Network in Pennsylvania	PI	1.8	7/1/05-12/31/07	$200,000 (total direct)
NCI/DCTC/CIP/DIB	Imaging Rapid Assessment Teams (IRATs) at the University of Pittsburgh Cancer Institute	Co-Investigator	1.2	9/1/05-8/31/08	$498,990 (total direct)
Genentech	Fludarabine, cyclo-phosphamine and rituximab for untreated patients with chronic lymphocytic leukemia	PI	9.0	9/1/04 – 6/30/08	$325,000 (total direct)
CLL – Topics	Safety and immuno-genicity of the TLR-7 agonist imiquimod as an immune adjuvant to pneumococcal polysaccharide vaccination in patients with untreated Rai stage 0-2 CLL	PI	2.0	7/06-1/08	$75,000 (total direct)
Bayer Healthcare/	Phase II clinical protocol	PI	6.0	9/06-	$250,000

Genentech	for the treatment of patients with previously untreated small lymphocytic lymphoma/chronic lymphocytic leukemia with a combination of fludarabine, cyclophosphamide and rituximab (FCR-Lite) followed by alemtuzumab			1/08	(total direct)
Oncovir, Inc.	Phase I study of intra-tumoral Poly-ICLC plus low dose local radiation in low grade recurrent B- and T-Cell Lymphoma	PI	6.0	9/06-6/08	To be Negotiated
Genentech	Relapsed/Refractory Chronic lymphocytic Leukemia (CLL) Patients Treated with lenalidomide (Revlimid®), rituximab (Rituxan®), and GM-CSF (Leukine®)	PI	3.0	10/06-6/08	To be determined (total direct)

2. Prior Grant Support

Louis Sklarow Memorial Fund, "Monoclonal Antibodies for B-Cell Lymphomas," Kenneth A. Foon, M.D., Principal Investigator, 7/1/86 - 6/31/87, $42,000 (total cost).

NIH 1 RO1 CA43212-01, "Mechanisms of Interferon Action in Hairy-Cell Leukemia," Kenneth A. Foon, M.D., Principal Investigator, 9/30/86 - 6/30/89, $173,960 (total direct cost).

NIH PO1 CA42768, "Radiopharmaceutical Diagnosis and Treatment of Cancer," Subproject: "Preclinical and Clinical Treatment with Monoclonal Antibodies to B-Cell Lymphomas," Kenneth A. Foon, M.D., Principal Investigator, 9/30/87 - 2/28/89, $265,803 (total direct cost).

"A Phase I/II Study of High-Dose, Continuous-Infusion Recombinant Human Interleukin-2 with Non-Small Cell Lung Cancer and Resistant Lymphoma," Kenneth A. Foon, M.D., Principal Investigator, Hoffmann La Roche, Inc., 10/1/88 - 9/30/89, $50,000 (total cost).

"A Phase I/II Clinical Investigation to Evaluate the Safety and Efficacy of Continuous Infusions of Recombinant Interleukin-2 and Phenylalanine Methyl Ester Pretreated Cells in Patients with Unresectable and/or Metastatic Melanoma and Renal Cell Cancer," Kenneth A. Foon, M.D., Principal Investigator, Dupont Corporation, 1/1/89 - 12/31/90, $270,000 (total cost).

NIH RO1 CA47860, "Idiotype Approach to Therapy of Human T-Cell Leukemia," Malaya Chatterjee, Ph.D., Principal Investigator, Kenneth A. Foon, M.D., Co-Investigator (10%), 4/1/89 - 3/31/92, $381,495 (total direct cost).

"Therapy of Renal Cell Carcinoma and Malignant Melanoma with Interleukin-2," Kenneth A. Foon, M.D., Principal Investigator (5%), Hoffmann La Roche, Inc., 6/1/90 - 5/31/91, $39,000 (total cost).

NIH 1PO1 CA4767-03 (Consortium), "Monoclonal Antibody Therapy of Breast Cancer," R. Ceriani, M.D., Program Director; "^{111}Indium-Labeled Monoclonal Antibody Imaging of Metastatic Breast Cancer," Kenneth A. Foon, M.D., Principal Investigator (5%), 1/2/91 - 8/31/91, $96,025 (total direct cost).

Buffalo Foundation Grant 857-0484A, "Feasibility Study of Anti-Idiotype Monoclonal Antibody Therapy for Patients with Cutaneous T-Cell Lymphoma," Kenneth A. Foon, M.D., Principal Investigator (5%), 3/1/91 - 2/29/92, $7,000 (total cost).

NIH 1PO1 CA58880-01A2 (Program Project Grant), "Monoclonal Antibody Therapy for GI Cancer," Kenneth A. Foon, M.D., Principal Investigator (20%), 9/1/91 - 8/31/94, $900,000 (total direct cost).

NIH RO1 CA54321-01 (Consortium), "Structure-Function of Tumor-Anti-Idiotype Antibodies," Heinz Köhler, M.D., Ph.D., Principal Investigator; "Generation of Tumor-Anti-Idiotypic Antibodies," Malaya Chatterjee, Ph.D., Principal Investigator, Kenneth A. Foon, M.D., Co-Investigator (10%), 7/1/91 - 6/30/94, $130,902 (total direct cost).

Share Foundation, "Phase Ib Study of Monoclonal Anti-Idiotype Antibody Therapy for Patients with Metastatic Melanoma," 1/1/93 - 12/31/95, $125,000 (total cost).
Ortho Pharmaceutical Corp. - Treatment of previously untreated chronic lymphocytic leukemia, 1994-95, $50,000.

Tobacco & Health, Anti-Idiotype Vaccine for Human Small Cell Lung Carcinoma, 7/1/94-6/30/95, $79,900 (total direct cost).

NCI 1PO1 CA57165-04 (Program Project Grant), "Monoclonal Antibody Therapy of GI Cancer", Kenneth A. Foon, M.D., Principal Investigator. Project 1. "Generation of Anti-Idiotype Tumor Vaccines", M. Chatterjee, Ph.D., Principal Investigator. 9/30/91 - 8/31/95, $768,027 (direct cost), $126,221 (indirect cost).

Berlex, Treatment of previously untreated low grade follicular lymphoma, Kenneth A. Foon, M.D., Principal Investigator, 1994-95, $51,000.

NCI 5U10 CA46136-07, Southwest Oncology Group Clinical Study, Kenneth A. Foon, M.D., Principal Investigator, 1/1/88 - 12/31/97, $507,164 (direct cost), $244,266 (indirect cost).

NIH R01 CA60000-02, Anti-Idiotype Vaccine for Breast Cancer, Kenneth A. Foon, M.D., Principal Investigator, 12/1/94 - 11/30/97, $477,406 (total direct cost), $233,929 (indirect cost).

P20-, Planning Grants for Prospective Cancer Centers, Kenneth A. Foon, M.D., Principal Investigator, 8/1/95 - 7/30/97, $350,000 (direct cost), $171,500 (indirect cost).

NIH NCI R01 CA72773-03, "Immunotherapy of Cancer with Anti-Id Based DNA Vaccines", Principal Investigator, Sunil K. Chatterjee, Ph.D., 10/01/99- 12/31/99.

Lucille P. Markey Charitable Trust, Research Program Grant, Kenneth A. Foon, M.D., Principal Investigator, 1/2/95 - 2/15/99, $1,900,000 (total direct cost).

NIH R03 CA79401-01, Anti-Idiotype Vaccine with IL-2 for Advanced Melanoma, Kenneth A. Foon, M.D., Principal Investigator,11/1/98 - 10/30/00, $145,646 (total direct and indirect cost).

Amgen, High Grade Lymphoma, Kenneth A. Foon, M.D., Principal Investigator, 2/1/95 - 2/1/99, $15,000 ($11,910 direct costs, $3,090 indirect cost).

NIH R01 CA72018-01, Ganglioside GD2 as Target for Immunotherapy in Melanoma, Kenneth A. Foon, M.D., Co-Investigator, 8/1/96 - 6/30/01, $1,142.854 (direct cost), $1,679,995 (total cost).

Titan Pharmaceutical, Inc., Anti-Idiotype Antibody Vaccines, Kenneth A. Foon, M.D., Co-Principal Investigator, 7/1/96 - 6/30/01, $1,750,000 (total direct cost).

NCI R03 CA72468-01, Comparison of Alum and QS-21 Based Anti-Idiotype Vaccines, Kenneth A. Foon, M.D., Principal Investigator, 12/1/96 - 11/30/98, $147,000 (direct and indirect cost).

NCI U01 CA65748-01, New Therapeutic Approaches to Breast Cancer, Kenneth A. Foon, M.D., Principal Investigator, 12/1/94 - 11/30/98, $842,019 (direct cost), $412,589 (indirect cost).

NIH NCI U01CA65748, "New Therapeutic Approaches to Breast Cancer", Principal Investigator, Kenneth A. Foon, M.D., 1/1/95 – 12/31/99.

NIH NCI R03 CA68629, "Comparison of Alum and QS-21 Based Anti-Id Vaccine", Principal Investigator Kenneth A. Foon, M.D., 11/01/96 – 10/31/99

NIH RO1 CA80968-01, "Anti-Idiotype Antibody Vaccine Therapy of Human Colorectal Cancer," Consultant, Kenneth A. Foon, MD, 9/1/99 - 7/31/03.

2. Seminars and invited lectureships related to your research. (Five years)

Anti-Idiotype Cancer Vaccines, The Children's Hospital Research Foundation Immunotherapy Conference, Cincinnati, OH, January 31, 2000.

Anti-Idiotype Antibodies Directed Against Gangliosides. Melanoma at the Millennium Conference, Phoenix, AZ, February 17, 2000

Anti-idiotype Vaccine that Mimics CEA: Novel therapeutic approach to colon cancer treatment. Case Western University, Ireland Cancer Center, Blood Club Seminar, Cleveland, OH, February 25, 2000.

Clinical and Immune Responses in Resected Colon Cancer patients Treated with Anti-Idiotype Monoclonal Antibody Vaccine that mimics the CarcinoembryonicAntigen. International Conference on Advances in Cancer Immunotherapy, Princeton, NJ, March 2 - 4, 2000.

Clinical and immune responses in resected colon cancer patients treated with anti-idiotype monoclonal antibody vaccine that mimics the carcinoembryonic antigen. 2nd Annual Walker's Cay Colloquium, Albert B. Sabin Vaccine Institute, Abaco, Bahamas, March 8 – 12, 2000.

The Barrett Cancer Center in the New Millennium. UC Board of Trustees, University of Cincinnati, Cincinnati, OH March 29, 2000.

Clinical Trials of Immunotherapeutics and Immunologic Monitoring. American Association for Cancer Research, April 3 – 4, 2000.

Targeted Therapies in the Treatment of Lymphoma, University of Louisville, Louisville, KY, Anti-idiotype Vaccine that Mimics the Carcinoembryonic Antigen. Dept. of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH April 20, 2000.

Cancer Vaccines. Sabin 40th Annual Anniversary Celebration, University of Cincinnati, Cincinnati, OH April 28, 2000.

The Barrett Cancer Center and the New Millennium. UC Medical Center Orientation, Cincinnati, OH May 4, 2000.

Non-Hodgkin's Lymphoma. Miami Valley Hospital Tumor Board, Dayton, OH May 5, 2000.

Colorectal Cancer: Molecular Genetics and Therapeutic Advances. University-Wide Clinical Pathology Conference, Cincinnati, OH May 10, 2000.

Cancer Vaccines. 2000 American Society of Clinical Oncology, New Orleans, LA. May 19 – 22, 2000

Vaccine Therapies of Malignant Melanoma. Hematology-Oncology Grand Rounds, University of Cincinnati, Cincinnati, OH. May 26, 2000.

Welcome and Introduction, Cancer Survivor's Day, University of Cincinnati, Cincinnati, OH, June 4, 2000.

Vaccine Approaches to the Adjuvant Treatment of Colorectal Cancer. The Barrett Cancer Center and University of Cincinnati Annual Cancer Conference. Cincinnati, OH June 17, 2000.

Chronic Lymphoid Leukemias. Hematology-Oncology Grand Rounds Conference, University of Cincinnati, Cincinnati, OH. September 29, 2000.

Overview of Immune Flow Cytometry of Leukemias and Lymphomas. The Barrett Cancer Center, University of Cincinnati College of Medicine, Cincinnati, OH. October 7, 2000.

An Update on Cancer Vaccines. 12th Annual Western North Carolina Cancer Conferennce, Asheville, North Carolina, October 27, 2000.

Rubitecan: An Effective New Therapy in Pancreatic Cancer. Chemotherapy Foundation Symposium XVIII, New York City, New York, November 8, 2000.

Vaccine in the Treatment of GI Malignancies. Gastrointestinal Cancer Research Conference 2000, Orlando, Florida, November 16 – 18, 2000.

Anti-Idiotype Antibody that Mimics Carcinoembryonic Antigen: Novel new Approach to Colon Cancer Immunotherapy. The Molecular Medicine of Colorectal Cancer, Keystone Symposia on Molecular and Cellular Biology, Taos, New Mexico, February 1 – 2, 2001.

Expanding Options in the Treatment of Non-Hodgkin's Lymphoma". Medical City Tumor Conference, Medical City Dallas Hospital, Dallas, TX. March 21, 2001.

Monoclonal Antibodies in Combination with Chemotherapy for the Treatment of Non-Hodgkin's Lymphoma. IDEC Pharmaceuticals Corporation, Dallas, TX. March 21, 2001.

Clinical Results: A Fully Human Anti-EGFr Antibody In Patients With Advanced Cancer: Molecular Targets and Cancer Therapeutics, AACR-NCI-EORTC International Conference. October 29 – November 2, 2001

Effects of ABX-EGF, A Fully Human Anti-EGFr Antibody, in Patients with Advanced Cancer. Cancer Research Institute Antibodies 2002 Symposium: New York, NY, March 19 – 20, 2002

Current Status of Vaccine Therapy in Malignancies. Moving Beyond The Ordinary; Fourth Annual Palm Beach Cancer Symposium, Delray Beach, FL., March 22-23, 2002.

ABX-EGF, A Fully Human Anti-Epidermal Growth Factor Receptor (EGFr) Monoclonal Antibody (MAb) In Patients With Advanced Cancer. Phase 1 Clinical Trials: American Society of Clinical Oncology: Gaylord Palms Resort and Convention Center, Kissimmee, FL. May 19 – 21, 2002.

ABX-EGF, A Fully Human Anti-Epidermal Growth Factor Receptor (EGFr) Monoclonal Antibody (MAb) for the Treatment of Patients with a Variety of EGFr Positive Malignancies. Anti-Cancer Drug Discovery & Development Summit 2002: Princeton, NJ, June 17 – 19, 2002.

ABX-EGF, A Fully Human Anti-EGFR Monoclonal Antibody For The Treatment Of Advanced Caner. First International Congress on Targeted Therapies: Washington, DC, August 16-18, 2002.

Monoclonal Antibodies/Other Immune Directed Strategies In Cancer Management. Emerging Therapeutics in Cancer: Update on Prostate Cancer, 7th Annual National VA Oncology Symposium, Alexandria, VA, October 2 – 4, 2002.

Nipent® (pentostatin) Experience in the Treatment of CLL. 2005 ASCO Annual Meeting, May 13-17, 2005.

International Vaccine Conference Anti-Idiotype Vaccines Mimicking the CEA and GD-2 Gangliosides, Italy, 2004.

Grand Rounds, University of Pittsburgh School of Pharmacy, Anti-Idiotype Vaccines Mimicking the CEA and GD-2 Gangliosides, Italy, 2004.

ECOG 2005 Fall Meeting, Anti-Idotype Antibody That Mimics the GD2 Gaglioside, Tampa, FL, Nov. 20, 2005.

Reason for Hope – Advances in the Treatment of CLL – "Reason to Hope" Series. UPMC St. Cancer Center – St. Clair, Upper St. Clair, PA, Nov. 30, 2005.

Early Results of Modified Fludarabine, Cyclophosphamide, and Rituximab (mFCR) for Patients with Previously Untreated Advanced Chronic Lymphocytic Leukemia (CLL), ASCO, June 2-6, 2006, Atlanta, GA, Co-Author.

Early Clinical and Pharmoacokinetic Results of Lower Dose Fludarabine and Cyclophosphamide, and High Dose Rituximab (FCR-Lite) for Paitnet swith Untreated Chronic Lymphocytic Leukemia (CLL), ASH, December 8-12, 2006, Co-Author & Presenter.

3. Other Research Related Activities

Patents

Tri-Gem (1A7)
Patent Number: 5,612,030
Date of Patent: 3/18/97
"Anti-idiotype monoclonal antibody 1A7 and use for the treatment of melanoma and small cell carcinoma"

TriAb (11D10)

Pending Serial Number: 08/766,350
Date Filed: 12/13/96
"Murine monoclonal anti-idiotype antibody 11D10 and methods of use thereof"

CeaVac (3H1)
Pending Serial Number: 08/579940
Date Filed: 12/28/95 (whole antibody)
"Murine monoclonal anti-idiotypic antibody 3H1"

Pending Serial Number: 08/579916
Date Filed: 12/28/95

Member, TVC Advisory Board	2006-present
Member, Spectrum Advisory Board	2006-present
Faculty, Berlex Speakers Bureau	2006-present
Faculty, Genentech Speakers Bureau	2006-present
Faculty, CBCE Speakers Bureau	2003-present
Esai Pharmaceutical Advisory Board	2003-present
Scientific Advisor, Automated Cell	2003-present
Supergen Scientific Advisory Board	2003-present
Editorial Board, Journal of Clinical Immunology	1993-present
Member, Scientific Advisory Board, National Surgical Adjuvant Breast and Bowel Project	1996-present
Editorial Board, Cancer Biotherapy & Radiopharmaceuticals	2005-present
Editor, Journal of Experimental Biology and Medicine, Translational Research Section	2005-present
Co-Editor, Expert Opinion on Biological Therapy, Future Perspectives Section	2006-present
Associate Editor, Clinical Cancer Research	1998-present

Editorial Board, Journal of Immunotherapy	1982-1996
Clinical Sciences Study Section (Subcommittee 4) Division of Research Grants	1986-1990
Associate Editor, Cancer Research	1987-2003
Associate Editor, Antibodies, Immunoconjugates and Radiopharmaceuticals	1987-1990
Editorial Board, Contemporary Oncology	1990-1994
Grants Review Committee for the American Cancer Society	1993-1996
Board of Directors, The Society for Biological Therapy	1995-1997
Editorial Board, Journal of Biotherapy	1995-2000
Board of Advisors, NeoRx Corporation, Seattle, WA	1985-1988
P01, Member, Memorial Sloan Kettering Cancer Center, NCI Site Visit committee, New York, NY	May 1, 1985
P01, Member, NCI Special Review Committee	October 1, 1985
P01, Member, Stanford Medical Center, NCI Site Visit Committee, Stanford, CA	October 1, 1985
National Research Service Award Advisory Committee, National Institute of Health	1985-1989
P01, University of California at Davis, Sacramento, CA, Member, NCI Site Visit Committee	March 1, 1988
P01, Member, Immunomedics, Site Visit Committee, Morris Plains, NJ	December 5, 1990
P01, Stanford Medical Center, Member, NCI Site Visit Committee, Stanford, CA	November 11, 1991

P30, Member, University of Nebraska Cancer Center, NCI Site Visit Committee, Omaha, NE	February 10, 1992
P50, Member, NCI Special Study Section for AIDS Center Grants	July 13, 1993
Board of Advisors, Inex Pharmaceuitcals Corp. Vancourver, B.C.	1994-1995
Health & Environment Laboratories, Eastman Kodak Company, Rochester, NY	1994-1996
PO1, University of California at Davis, Sacramento, CA, NCI Site Visit Committee Chairman	April 13, 1994
2P01CA59326-03, Gene Therapy for Cancer, University of California at Los Angeles, Member, NCI Site Visit Committee	June 19, 1994
Scientific Review Panel, Israel Cancer Research Fund, New York, NY	1995-2001
2P01CA4499108, Theray of Lymphoma/Leukemia with Monoclonal Antibodies, Fred Hutchinson Cancer Research Center, Member, NCI Site Visit Committee	February 14, 1995
1P30CA6953301, Oregon Cancer Center, Member, NCI Site Visit Committee	June 12, 1995
1P30CA6953301, Oregon Cancer Center, Member NCI Site Visit Committee	August 3, 1995
NSABP Scientific Advisory Board, Operations Center Site Visit, Pittsburgh, PA	February 6, 1996
2P01CA5935005, Memorial-Sloan Kettering Cancer Center, Gene Therapy Program, NCI Site Visit Committee Chairman	July 7, 1996
1P30CA6953301A1 Oregon Cancer Center, Member, NCI Site Visit Committee	October 7, 1996
Director, Scientific Advisory Board, Titan Pharmaceuticals, Inc., South San Francisco, CA	1996-2001

NCI Scientific Review Group-Subcommittee H	1997-2001
NCI Clinical Oncology Study Section	1999-2001
ACOSOG Site Visit, Chicago, IL	Sept. 21, 1999
SuperGen Advisory Board Meeting, Phoenix, AZ	January 15, 2000
SuperGen Advisory Board Meeting, Phoenix, AZ	January 13-16, 2000
NCI GI Intergroup State-of-Science Symposium	February 15, 2000
NCI Clinical Oncology Study Section, Bethesda, MD	March 20, 2000
IDEC Pharmaceuticals Meeting, San Diego CA	May 7-8, 2000
American College of Surgeons/Tritan Pharmaceutical Meeting, Chicago, IL	May 16, 2000
NCI NIH Scientific Review Group-Subcommittee H Site Review, Rochester, MN	June 7-9, 2000
SuperGen, Rubitecan Advisory Board Meeting Maui, HI	June 13-17, 2000
American College of Surgeons Semiannual Meeting, Chicago, IL	June 24, 2000
NCI Clinical Oncology Study Section, Bethesda, MD	July 7-14, 2000
Abbott Pharmaceutical Advisory Panel, Chicago, IL	Dec. 8-9-, 2000
Fulcrum Renal Cell Advisory Board Mtg. New York	Jan. 14-15, 2001
NCI Breast Intergroup Retreat, Washington, DC	Jan. 18-19, 2001
NCI Scientific Review Group-Subcommittee H Teleconference	March 15, 2001

PO1, Member, NCI Scientific Review Group November 2005

ICRF Scientific Review Group March 2006

LIST OF CURRENT RESEARCH INTERESTS:

Current grant funded research is a phase III clinical trial using the TriGem anti-idiotype vaccine for melanoma developed in our laboratories. At the UPCI, I am developing new protocols for a variety of hematologic malignancies including Hodgkin's disease, lymphomas, chronic lymphocytic leukemia, multiple myeloma, chronic myelogenous leukemia, acute myelogenous leukemia, and myelodysplastic syndromes. A collaboration with the NCI and Therion Biopharm for a vaccine therapy of CLL has been established. New collaborations with UPCI investigators are ongoing to generate dendritic cell vaccines for B-cell lymphoma and multiple myeloma. We have established a chronic lymphoid malignancies/multiple myeloma clinical center that will allow us to expand these translational research programs. In the area of solid tumors, we are establishing new areas of translational research with UPCI investigators generating a variety of dendritic cell vaccine approaches, and with investigators at the National Cancer Institute and Biotechnology companies using viral vectors for gene therapy.

SERVICE:

1. University and Medical School

1989 - 1990	Search Committee for Chairman, Department of Radiation Oncology, Roswell Park Cancer Institute
1989 - 1990	Search Committee for Chairman, Department of Cytogenetics, Roswell Park Cancer Institute
1999 –2001	Oncology-Hematology Care Executive Committee, University of Cincinnati
1999 –2001	Ohio Cancer Incidence Surveillance System Advisory Board Ohio Department of Health
1999 –2001	Hematology-Oncology Fellow Evaluation Committee, University of Cincinnati
1989 - 1990	Search Committee for Chairman, Department of Pediatrics, Roswell
1990	Head, Search Committee for Infectious Disease Specialist, Roswell Park Cancer Institute
1990 - 1991	Search Committee for Chairman, Department of Microbiology, SUNY
1989 - 1990	Radiation Safety Committee, Roswell Park Cancer Institute
1989 - 1990	Quality Assurance Committee, Roswell Park Cancer Institute
1989 - 1991	American Society of Hematology, Neoplastic Committee
1990	Head, Search Committee for Pulmonologist/Intensivist, Roswell Park

1991	Head, Search Committee for Cardiologist, Roswell Park Cancer Institute Cancer Institute
1990 - 1991	Vice President, Medical Staff, Roswell Park Cancer Institute
1993	Head, Search Committee for Chairman of Radiation Medicine,
1989 - 1991	American Society of Clinical Oncology, Program Committee
1991 - 1992	American Association for Cancer Research, Program Committee
1992 - 1994	Clinical Immunology Society, Program Committee
1992 -1989	Internal Medicine Chairman's Advisory Committee
1994 –1999	Liaison Committee on Medical Education, University of Kentucky
1994 - 1996	Medical Center Clinical Sciences Area Advisory Committee, University of Kentucky
1996 - 1999	General Clinical Research Center Advisory Committee, University of Kentucky
1999 –2001	Chair, Cancer Steering Committee, University Hospital, University of Cincinnati
1999 –2001	Vontz Steering Committee, University of Cincinnati
1999 –2001	Chair, Internal Advisory Committee, Barrett Cancer Center, University of Cincinnati
1999 –2001	Chair, Scientific Review Committee, Barrett Cancer Center, University of Cincinnati
2003-Present	Director of the University of Pittsburgh Cancer Institute, GCRC
2003-Present	Member of the University of Pittsburgh Medical Center GCRC Advisory Board
2005-Present	Co-Chair, PAC3, Pennsylvania Cancer Control Consortium
2003-Present	Co-Leader, Biologic Therapeutics Program, University of Pittsburgh
2003-Present	Co-Leader, Hematologic Malignancy Program, University of Pittsburgh
2003-Present	Director of Clinical Investigations, University of Pittsburgh Cancer Institute

2. Community Activities

1985-1987	Board of Trustees, Michigan Chapter, Leukemia Society of America
1994-1995	American Cancer Society, Board of Directors, Fayette County Unit
1994 - 1996	Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY
1998	Department of Insurance, Commonwealth of Kentucky

SPECIAL ANNOUNCEMENT

CD Antigens 1989

By W. Knapp, B. Dörken, P. Rieber, R.E. Schmidt, H. Stein, and A.E.G.Kr. von dem Borne

At the recently held Fourth International Workshop and Conference on Human Leukocyte Differentiation Antigens, agreement was reached* on 35 new CD clusters and subclusters. In addition, seven previously established clusters were redefined. The following summary table should provide the reader with an up-to-date list of all presently accepted CD designations† and some basic information concerning the molecules defined by these antibodies. Detailed reports will be published separately,‡ as will a new database/evaluation program,§ which should allow individual scientists to directly compare the specificities of new antibodies with the characteristics of all antibodies from the Third and Fourth International Workshop.

CD Design	Selection of Assigned Monoclonal Antibodies	Main Cellular Reactivity	Recognized Membrane Component‖	Sequence/ CH-Structure Analyzed¶
CD1a	NA1/34; T6; VIT6; Leu6	Thy, DC, B subset	gp49	Y
CD1b	WM-25; 4A76; NUT2	Thy, DC, B subset	gp45	Y
CD1c	L161; M241; 7C6; PHM3	Thy, DC, B subset	gp43	Y
CD2	9.6; T11; 35.1	T	CD58 (LFA-3) receptor, gp50	Y
CD2R	T11.3; VIT13; D66	Activated T	CD2 epitopes restr. to activ. T	Y
CD3	T3; UCHT1; 38.1; Leu4	T	CD3-complex (5 chains),gp/p 26,20,16	Y
CD4	T4; Leu3a; 91.D6	T subset	Class II/HIV receptor, gp59	Y
CD5	T1; UCHT2; T101; HH9; AMG4	T, B subset	gp67	Y
CD6	T12; T411	T, B subset	gp100	–
CD7	3A1; 4A; CL1.3; G3-7	T	gp40	Y
CD8	Alpha-chain: T8; Leu2a; M236; UCHT4; T811	T subset	Class I receptor, gp32α, / or /β dimer	Y
	beta-chain: T8/2T8-5H7			Y
CD9	CLB-thromb/8; PHN200; FMC56	Pre-B, M, Plt	p24	–
CD10	J5, VILA1, BA-3	Lymph.Prog., cALL, Germ Ctr. B, G	Neutral endopeptidase, gp100, CALLA	Y
CD11a	MHM24; 2F12; CRIS-3	Leukocytes	LFA-1, gp180/95	Y
CD11b	Mo1; 5A4.C5; LPM19C	M, G, NK	C3bi receptor, gp155/95	–
CD11c	B-LY6; L29; BL-4H4	M, G, NK, B sub	gp150/95	–
CDw12	M67	M, G, Plt	(p90-120)	–
CD13	MY7, MCS-2, TÜK1, MOU28	M, G	Aminopeptidase N, gp150	Y
CD14	Mo2, UCHM1, VIM13, MoP15	M, (G), LHC	gp55	Y
CD15	My1, VIM-D5	G, (M)	3-FAL, X-Hapten	Y
CD16	BW209/2; HUNK2; VEP13; 3G8	NK, G, Mac.	FcRIII, gp50-65	Y
CDw17	GO35, Huly-m13	G, M, Plt	Lactosylceramide	–
CD18	MHM23; M232; 11H6; CLB54	Leukocytes	β-chain to CD11a,b,c	Y
CD19	B4; HD37	B	gp95	Y
CD20	B1; 1F5	B	p37/32, Ion channel?	Y
CD21	B2; HB5	B subset	C3d/EBV-Rec. (CR2), p140	Y
CD22	HD39; S-HCL1; To15	Cytopl. B/surface B subset	gp135, homology to myelin assoc. gp (MAG)	Y
CD23	Blast-2, MHM6	B subset, act.M, Eo	FceRII, gp45-50	Y
CD24	VIBE3; BA-1	B, G	gp41/38?	–
CD25	TAC; 7G7/B6; 2A3	Activated T, B, M	IL-2R βchain, gp55	Y
CD26	134-2C2; TS145	Activated T	Dipeptidylpeptidase IV, gp120	Y
CD27	VIT14; S152; OKT18A; CLB-9F4	T subset	p55 (dimer)	–
CD28	9.3; KOLT2	T subset	gp44	Y
CD29	K20; A-1A5	Broad	VLA β-, integrin β1-chain, Plt GPIIa	Y
CD30	Ki-1; Ber-H2; HSR4	Activated T, B; Sternberg-Reed	gp120, Ki-1	–
CD31	SG134; TM3; HEC-75; ES12F11	Plt, M, G, B, (T)	gp140, Plt. GPIIa	–
CDw32	CIKM5; 41H16; IV.3; 2E1; KB61	M, G, B, Plt	FcRII, gp40	Y
CD33	My9; H153; L4F3	M, Prog., AML	gp67	Y
CD34	My10, BI-3C5, ICH-3	Prog	gp105-120	Y

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CD Design	Selection of Assigned Monoclonal Antibodies	Main Cellular Reactivity	Recognized Membrane Component‖	Sequence/ CH-Structure Analyzed¶
CD35	TO5, CB04, J3D3	G, M, B	CR1	Y
CD36	5F1, CIMeg1; ESIVC7	M, Plt, (B)	gp90, Plt GPIV	-
CD37	HD28; HH1; G28-1	B, (T,M)	gp40-52	Y
CD38	HB7; T16	Lymph.Prog., PC, Act. T	p45	Y
CD39	AC2; G28-2	B subset, (M)	gp70-100	-
CD40	G28-5	B, carcinomas	gp50, Homology to NGF-Receptor	Y
CD41	PBM 6.4; CLB-thromb/7; PL273	Plt	Plt GPIIb/IIIa complex and GPIIb	Y
CD42a	FMC25; BL-H6; GR-P	Plt	Plt GPIX, gp23	Y
CD42b	PHN89; AN51; GN287	Plt	Plt GPIb, gp135/25	Y
CD43	OTH 71C5; G19-1; MEM-59	T, G, M, brain	Leukosialin, gp95	Y
CD44	GRHL1; F10-44-2; 33-3B3; BRIC35	T, G, M, brain, RBC	Pgp-1, gp80-95	Y
CD45	T29/33; BMAC 1;AB187	Leukocytes	LCA, T200	Y
CD45RA	G1-15; F8-11-13; 73.5	T subset, B, G, M	Restricted T200, gp220	Y
CD45RB	PTD/26/16	T subset, B, G, M	Restricted T200	Y
CD45RO	UCHL1	T subset, B, G, M	Restricted T200, gp180	Y
CD46	HULYM5; 122-2; J4B	Leukocytes	Membrane cofactor protein (MCP), gp66/56	Y
CD47	BRIC 126; CIKM1; BRIC 125	Broad	gp 47-52, N-linked glycan	-
CD48	WM68; LO-MN25; J4-57	Leukocytes	gp41, PI-linked	-
CDw49b	CLB-thromb/4; Gi14	Plt, cultured T	VLA-alpha2-chain, Plt GPIa	Y
CDw49d	B5G10; HP2/1; HP1/3	M, T, B,(LHC), Thy	VLA-alpha4-chain, gp150	-
CDw49f	GoH3	Plt, (T)	VLA-alpha6-chain, Plt GPIc	-
CDw50	101-1D2; 140-11	Leukocytes	gp148/108, PI-linked	-
CD51	13C2; 23C6; NKI-M7; NKI-M9	(Plt)(B)	VNR alpha-chain	Y
CDw52	097; YTH66.9; Campath-1	Leukocytes	Campath-1, gp21-28	-
CD53	MEM-53; HI29; HI36; HD77	Leukocytes	gp32-40	-
CD54	RR7/7F7; WEHI-CAMI	Broad, Activ.	ICAM-1	Y
CD55	143-30; BRIC 110;BRIC 128; F2B-7.2	Broad	DAF (decay accelerating factor), PI-linked	Y
CD56	Leu19; NKH1; FP2-11.14, L185	NK, activ.lymphocytes	gp220/135, NKH1, isoform of N-CAM	Y
CD57	Leu7; L183; L186	NK, T, B sub, Brain	gp110, HNK1	-
CD58	TS2/9; G26; BRIC 5	Leukocytes, Epithel	LFA-3, gp40-65, PI-linked	Y
CD59	YTH53.1; MEM-43	Broad	gp18-20, PI-linked	-
CDw60	M-T32; M-T21; M-T41; UM4D4	T sub	NeuAc-NeuAc-Gal-	Y
CD61	Y2/51; CLB-thromb/1; VI-PL2; BL-E6	Plt	Integrin β3-, VNR β-chain, Plt GPIIIa	Y
CD62	CLB-thromb/6; CLB-thromb/5; RUU-SP1.18.1	Plt activ.	GMP-140 (PADGEM), gp140	Y
CD63	RUU-SP2.28; CLB-gran/12	Plt activ., M, (G, T, B)	gp 53	-
CD64	Mab32.2; Mab22	M	FcRI, gp75	Y
CDw65	VIM2; HE10; CF4; VIM8	G, M	Ceramide-dodecasaccharide 4c	Y
CD66	CLB gran/10; YTH71.3	G	Phosphoprotein pp180-200	-
CD67	B13.9; G10F5; JML-H16	G	p100, PI-linked	-
CD68	EBM11; Y2/131; Y-1/82A; Ki-M7; Ki-M6	Macrophages	gp110	-
CD69	MLR3; L78; BL-Ac/p26; FN50	Activated B, T	gp32/28, AIM	-
CDw70	Ki-24; HNE 51; HNC 142	Activated B, -T, Sternberg-Reed cells	Ki-24	-
CD71	138-18; 120-2A3; MEM-75; VIP-1; Nu-TfR2	Proliferating cells, Mac.	Transferrin receptor	Y
CD72	S-HCL2; J3-109; BU-40;BU-41	B	gp43/39	-
CD73	1E9.28.1; 7G2.2.11; AD2	B subset, T subset	ecto-5'-nucleotidase, p69	-
CD74	LN2; BU-43; BU-45	B, M	Class II assoc. invariant chain, gp 41/35/33	-
CDw75	LN1; HH2; EBU-141	Mature B, (T subset)	p53?	-
CD76	HD66; CRIS-4	Mature B, T subset	gp 85/67	-
CD77	38.13(BLA); 424/4A11; 424/3D9	Restr. B	Globotriaosylceramide (Gb3)	-
CDw78	Anti Ba; LO-panB-a; 1588	B, (M)	?	-

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†To be approved by the IUIS/WHO Nomenclature Committee.

‡In Leucocyte Typing IV, W. Knapp, B. Dörken, P. Rieber, R.E. Schmidt, H. Stein, A.E.G.Kr. von dem Borne (eds). Oxford University Press, Oxford 1989 (in press)

§Leucocyte Typing IV Database and Evaluation Programme, Oxford University Press (in preparation)

‖Abbreviations: Thy, thymocytes; DC, dendritic cells; B, B cells; T, T cells; M, monocytes; G, granulocytes; Plt, platelets; Prog, progenitor cells; Germ.Ctr.B., germinal centre B cells; NK, NK cells; Mac, macrophages; cytopl., cytoplasmic; LHC, epidermal Langerhans cells.

¶Y, for protein antigens: sequence data available, for carbohydrate antigens: reactive oligosaccharide structure known.

UPDATE

CD ANTIGENS 1993

S. F. Schlossman, L. Boumsell, W. Gilks, J. M. Harlan, T. Kishimoto, C. Morimoto, J. Ritz, S. Shaw, R. L. Silverstein, T. A. Springer, T. F. Tedder, and R. F. Todd

The results of the 5th International Workshop on Human Leukocyte Differentiation Antigens were presented on November 3 through 7, 1993 at a conference held in Boston. Those present at this meeting represent the efforts of more than 500 laboratories worldwide, who have joined together over a two-year period to analyze 1450 antibodies and characterize over 150 molecules. Blind panels for all mAbs, including every CD, every known candidate for CD status, and all mAbs of undefined specificity were analyzed by flow cytometry. Other dedicated laboratories undertook serologic, molecular, biochemical, and histochemical characterization of the mAbs and the structures they defined. The results obtained by all groups showed almost perfect concordance. Detailed results of these studies will be published separately (1). In addition, a Leukocyte Differentiation Antigen Database (LDAD) has been developed to 1) provide identifying information on all molecules and mAbs studied in the workshop; and 2) display and analyze quantitative expression of each molecule on more than 80 cell types[1]. Based on these findings, the workshop organizers are pleased to recommend the adoption of 48 new CD clusters and subclusters and the redefinition of 14 previously established clusters. The following table summarizes the additions and changes made to the existing CD nomenclature.

References

1. Schlossman, S. F., L. Boumsell, W. Gilks, J. M. Harlan, T. Kishimoto, C. Morimoto, J. Ritz, S. Shaw, R. L. Silverstein, T. A. Springer, T. F. Tedder, and R. F. Todd, eds. 1994. In press. *Leucocyte Typing V: White Cell Differentiation Antigens.* Oxford University Press, Oxford.

[1] The LDAD program runs on IBM PCs and via emulation on Macintosh. It may be downloaded freely by anonymous ftp from balrog.nci.nih.gov (156.40.182.2) or purchased on disk (inquire by FAX (301) 480–2052).

Table I. CD antigens 1993

CD Designation	Common Name	Workshop Section	MW Reduced
CD15s	sLe^x, Sialyl Lewis^x	ADHESION	
CD16	FcR IIIA/FcR IIIB	MYELOID	50–65
CD16b	FcR IIIB	MYELOID	48
CD32	Previously CDw32, FcRII	MYELOID	40
CD42a	GPIX	PLATELETS	23
CD42b	GPIB, α	PLATELETS	135, 23
CD42c	GP1B-β	PLATELETS	22
CD42d	GPV	PLATELETS	85
CD44	Pgp-1	ADHESION	80–90
CD44R	Restricted epitope on CD44	ADHESION	
CD49a	VLA-1, α1integrin chain	ADHESION	210
CD49b	VLA-2, α2 integrin chain	ADHESION	160
CD49c	VLA-3, α3 integrin chain	ADHESION	125
CD49d	VLA-4, α4 integrin chain	ADHESION	150, 80, 70
CD49e	VLA-5, α5 integrin chain	ADHESION	135, 25
CD49f	VLA-6, α6 integrin chain	ADHESION	120, 25
CD50	ICAM-3	ADHESION	124
CD51/CD61	Complex dependent epitope	ADHESION	
CD52	Campath-1	BLIND	21–28
CD62E	E-selectin, ELAM-1	ADHESION	115
CD62L	L-selectin, LAM-1, TQ-1	ADHESION	75–80

0022-1767/94/$02.00

Table I. *Continued*

CD Designation	Common Name	Workshop Section	MW Reduced
CD62P	P-selectin, GMP-140, PADGEM	ADHESION	150
CD66a	BGP	MYELOID	180–200
CD66b	CD67, p100, CGM6	MYELOID	95–100
CD66c	NCA	MYELOID	90–95
CD66d	CGM1	MYELOID	30
CD66e	CEA, carcinoembryonic antigen	MYELOID	180–200
CD67	Now CD66b		
CD70	CD27-ligand	ACTIVATION	55, 75, 95, 110, 170
CDw76	Previously CD76	B CELL	NA
CD79a	mb-1, Igα	B CELL	33, 40
CD79b	B29, Igβ	B CELL	33, 40
CD80	B7, BB1	B CELL	60
CD81	TAPA-1	B CELL	22
CD 82	R2, IA4, 4F9	B CELL	50–53
CD83	HB15	B CELL	43
CDw84		B CELL	73
CD85	VMP-55, GH1/75	B CELL	120, 83
CD86	FUN-1, BU63	B CELL	80
CD87	UPA-R	MYELOID	50–65
CD88	C5aR	MYELOID	42
CD89	FcαR	MYELOID	55–75
CDw90	Thy-1	MYELOID	25–35
CD91	α^2M-R	MYELOID	600
CDw92		MYELOID	70
CD93		MYELOID	120
CD94	KP43	NK CELL	43
CD95	APO-1, FAS	ACTIVATION	42
CD96	TACTILE	ACTIVATION	160
CD97		ACTIVATION	74, 80, 89
CD98	4F2, 2F3	T CELL	80, 40
CD99	E2, MIC2	T CELL	32
CD99R	CD99 mAb restricted	T CELL	32
CD100	BB18, A8	T CELL	150
CDw101	BB27, BA27	T CELL	140
CD102	ICAM-2	ADHESION	60
CD103	HML-1	ADHESION	150, 25
CD104	β4 integrin chain	ADHESION	220
CD105	Endoglin	ENDOTHELIAL	95
CD106	VCAM-1, INCAM-110	ENDOTHELIAL	100, 110
CD107a	LAMP-1	PLATELET	110
CD107b	LAMP-2	PLATELET	120
CDw108		ADHESION	80
CDw109	8A3, 7D1	ENDOTHELIAL	170/150
CD115	CSF-1R; M-CSFR	MYELOID	150
CDw116	HGM-CSFR, GM-CSFR	CYTOKINE	75–85
CD117	SCFR, cKIT	CYTOKINE	145
CDw119	IFNγR	CYTOKINE	90
CD120a	TNFR; 55kD	CYTOKINE	55
CD120b	TNFR; 75KD	CYTOKINE	75
CDw121a	IL-1R; Type 1	CYTOKINE	80
CDw121b	IL-1R; Type 2	CYTOKINE	68
CD122	IL-2R; 75KD, IL-2Rβ	CYTOKINE	75
CDw124	IL-4R	CYTOKINE	140
CD126	IL-6R	CYTOKINE	80
CDw127	IL-7R	CYTOKINE	75
CDw128	IL-8R	CYTOKINE	58–67
CDw130	IL-6R-gp130SIG	CYTOKINE	130

0022-1767/80/1254-1678$02.00/0
THE JOURNAL OF IMMUNOLOGY

Vol. 125, No. 4, October 1980
Printed in U.S.A.

CHARACTERIZATION OF A HUMAN B LYMPHOCYTE-SPECIFIC ANTIGEN[1]

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A human B lymphocyte-specific antigen (B1) was identified and characterized by the use of a monoclonal antibody. By indirect immunofluorescence, cytotoxicity, and quantitative absorption, B1 was present on approximately 9% of the peripheral blood mononuclear cell fraction and >95% of B cells from blood and lymphoid organs in all individuals tested. Monocytes, resting and activated T cells, null cells, and tumors of T cell and myeloid origin were B1 negative. B1 was distinct from standard B cell phenotypic markers, including Ig and Ia antigen. Removal of the B1 positive population in peripheral blood eliminated all B cells capable of responding to pokeweed mitogen by maturation to Ig-producing cells.

Human B lymphocytes possess a distinct cell surface phenotype that distinguishes them from other lymphoid cell populations. These markers include integral membrane immunoglobulin (Ig) (1), receptors for C3 and the Fc portion of IgG (2, 3), and the presence of antigens encoded by the HL-A-D locus, the so-called DR antigens (4–8). The latter appear to be biochemically and functionally analogous to murine I-E/C region (Ia) antigens (9, 10).

However, because many of these phenotypic markers are not restricted in their expression to B cells, their utility in cell enumeration and fractionation is somewhat limited. Distinction between B cells and monocytes presents particular difficulties, since the latter also bear Fc and C3 receptors (11) and Ia antigen (12, 13), and may bind Ig via their Fc receptors, producing false Ig positivity (14). In addition, Fc receptors may be present on a subset of T cells (15), and T cells have been shown to express Fc receptors (16) and Ia antigens (17, 18) subsequent to activation.

A phenotypic marker with representation limited to B lymphocytes would therefore be extremely useful in the enumeration, fractionation, and analysis of function of the B cell population. Heteroantisera with B cell specificity have previously been described, produced by cross-species immunization and extensive absorption with non-B cell lines and tumors. Some of these antisera appear to define B cell-specific alloantigens (19–23), although many have been found to be principally directed against HL-A-D locus antigens (m.w. 29,000 and 34,000) (5–8, 12), and are thus also present on monocytes and other cell types (24).

In the present investigation, a monoclonal antibody specific for human B cells is described and characterized. This antibody was found to define an antigen (B1) present on approximately 9% of peripheral blood mononuclear cells (PBM)[3] and >95% of peripheral blood B cells from all individuals tested. B1 was found to be unrelated to known phenotypic markers of B cells, including Ig and known Ia antigens. Functional studies demonstrated that removal of the B1-positive population from peripheral blood by cell sorting or complement-(C) mediated lysis, eliminated the cell population that is induced to differentiate into Ig-secreting plasma cells in a pokeweed mitogen-(PWM) driven system.

MATERIALS AND METHODS

Immunization and somatic cell hybridization. A 6-week-old female BALB/c mouse (Jackson Laboratories, Bar Harbor, ME) was immunized i.p. with 5×10^6 cryopreserved Burkitt's lymphoma tumor cells in phosphate-buffered saline (PBS). Twenty-eight days later, the mouse was boosted with 5×10^6 tumor cells i.v., and somatic cell hybridization was carried out 4 days later by the method of Kohler and Milstein (25), with modifications (26). Mouse splenocytes (1.5×10^8) were fused in 30% polyethylene glycol (PEG) and Dulbecco's MEM with 2×10^7 P3/NS1/1-Ag4-1 myeloma cells (kindly provided by Dr. R. Kennett, University of Pennsylvania, Philadelphia, PA).

Selection and growth of hybridomas. After fusion, cells were cultured in HAT medium (hypoxanthine, aminopterin, and thymidine) at 37°C in a 5% CO_2 humid atmosphere (27). Fourteen to 28 days later, 100 μl of supernatant from cultures exhibiting cell growth were tested for the presence of hybridoma antibodies reactive with the immunizing Burkitt's tumor cell by indirect immunofluorescence as previously described (28). In brief, 10^6 cells were incubated with culture supernatants at 4°C for 20 min, washed twice with medium, and stained with a fluoresceinated goat anti-mouse IgG (G/M FITC) (Meloy Laboratories, Springfield, VA) for 20 min on ice. After an additional 2 washes, fluorescent antibody-coated cells were analyzed on a fluorescence-activated cell sorter (FACS-I) (Becton Dickinson, Mountain View, CA), or a cytofluorograf FC200/4800A (Ortho

Received for publication March 20, 1980.
Accepted for publication June 2, 1980.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] This work was supported by National Institutes of Health Grants DE-04881, AI 12069, CA 19589, CA 06516, and RR 05526.
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[3] Abbreviations used in this paper: CLL; chronic lymphatic leukemia; D-PDL, diffuse, poorly-differentiated lymphoma; E+, sheep erythrocyte positive; FACS, fluorescence-activated cell sorter; G/M FITC, fluorescein-conjugated goat anti-mouse IgG; PBM, peripheral blood mononuclear cells; PEG, polyethylene glycol; PWM, pokeweed mitogen; RIA, radioimmunoassay; sIg+, surface Ig positive; TCM, tissue culture medium; DMSO, dimethyl sulfoxide; HEPES, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid.

Instruments, Westwood, MA). Hybridoma cultures containing antibodies reactive with the immunizing tumor were selected and cloned by the limiting dilution method in the presence of feeder cells (29). Recloned hybridomas were subsequently maintained by injection of 1×10^6 cells i.p. into BALB/c mice primed with pristane (Aldrich Chemical Co., Milwaukee, WI). Monoclonal antibody-containing ascites were used in all subsequent experiments.

Isolation of lymphocyte populations. Human PBM were isolated from healthy volunteer donors by Ficoll-Hypaque density gradient centrifugation (Pharmacia Fine Chemicals, Piscataway, NJ) (30). Unfractionated mononuclear cells were separated into surface Ig-positive (sIg+) (B) and sIg− (T plus null) populations by Sephadex G-200 anti-$F(ab')_2$ chromatography (31), with modifications designed to minimize monocyte retention by the column. In brief, purified rabbit anti-human $F(ab')_2$ was pepsin-digested and chromatographed on Sephadex G-150 to remove undigested material. The $F(ab')_2$ anti-human $F(ab')_2$ fragments were then coupled to CNBr-activated Sephadex G-200. PBM were preincubated at 37°C for 1 hr to remove cytophilically-bound serum IgG (32), and cells were then applied to the anti-$F(ab')_2$ column and fractionated as outlined previously (31). The sIg+ (B) population was obtained from the Sephadex G-200 column by competitive elution with normal human γ-globulin. B cell preparations were routinely >90% sIg+, <5% E+, and contained approximately 5% monocytes as judged by morphology, latex ingestion, and reactivity with the monocyte-specific monoclonal antibody OKM1 (33). T cells were recovered by E rosetting the sIg− population with 5% sheep erythrocytes (Microbiological Associates, Bethesda, MD). The rosetted mixture was layered over Ficoll-Hypaque, and the recovered E+ pellet was treated with 0.155 M NH_4Cl to lyse erythrocytes. The T cell population obtained was <2% sIg+ by methods previously described (34). Normal human monocytes were obtained by adherence to plastic culture dishes as previously described (28). For determination of the reactivity of anti-B1, 1×10^6 of each cell population was subjected to indirect immunofluorescence analysis as described above.

In experiments designed to separate B1+ and B1− cells, 100×10^6 unfractionated PBM were labeled with 4 ml of a 1/100 dilution of anti-B1 and developed with G/M FITC. Cells were then separated on a FACS-I into B1+ (8.3% of PBM) and B1− populations. All fractions were washed 3 times and placed into culture for functional studies.

Normal human tissue. After appropriate Human Protection Committee validation and informed consent, human specimens were obtained during surgery. Nucleated bone marrow cells were recovered by Ficoll-Hypaque centrifugation. Tonsil cells were obtained at the time of routine tonsillectomy. Lymph node tissue was taken for diagnostic biopsy, and was considered normal based on histology and cell surface markers. Splenocytes were obtained at the time of traumatic rupture. Normal human thymocytes were obtained from patients who had portions of their thymuses removed during corrective cardiac surgery. All tissue specimens were immediately placed in media containing 5% fetal calf serum (FCS), finely minced with forceps and scissors, and made into single-cell suspensions by extrusion through stainless steel mesh. Cell samples were cryopreserved and thawed as needed.

Cell lines and leukemia and lymphoma tumor cells. Epstein-Barr virus- (EBV) transformed B lymphoblastoid lines (SB, Laz 007, 234, 296, 388, and 444), T cell lymphoblastoid lines (CCRF-CEM and HSB-2), Null cell leukemia line Laz 221, and Burkitt's lines Daudi, Ramos, and Raji were kindly provided by Dr. Herbert Lazarus (Sidney Farber Cancer Institute, Boston, MA). Tumor cells were obtained from 19 patients with acute and chronic leukemias, and 12 patients with various forms of non-Hodgkin's lymphomas. In all instances, the tumor populations utilized contained more than 90% blasts by Wright-Giemsa morphology. B cell lineage was established by the presence of a) monoclonal sIg, as determined by indirect immunofluorescence utilizing an anti-λ or anti-κ hybridoma antibody (kindly donated by Dr. V. Raso, Sidney Farber Cancer Institute, manuscript in preparation); b) Fc and/or C3 receptors (2, 3); c) Ia antigen, by reactivity with a heterologous anti-p23,30 antiserum (8), or a monoclonal antibody of broad specificity directed against an Ia framework determinant designated I-2 (L. Nadler, manuscript in preparation). I-2 has been shown to react with B cells, adherent monocytes, and Con A-activated T cells (but not resting T cells) from 20/20 randomly selected normal individuals. In addition, I-2 reacts with homozygous typing cells encompassing all DR specificities (DR1-DR11) (cells kindly provided by Dr. Edmund Yunis, Division of Immunogenetics, SFCI). Biochemical studies (performed by Dr. John Pesando, SFCI) have demonstrated that I-2 precipitates a bimolecular complex of m.w. 29,000 and 34,000. T cell tumors were identified by spontaneous E rosette formation (>20%) and reactivity with the specific T cell antibody OKT3 (35). A total of 18 B cell tumors, including 6 chronic lymphatic leukemias (CLL), 8 diffuse, poorly differentiated lymphomas (D-PDL), and 4 nodular lymphomas were assessed for presence of B1 antigen. T cell tumors included 2 CLLs, 4 acute lymphoblastic leukemias, and 1 D-PDL. All tumor cells were cryopreserved in −196°C vapor phase nitrogen in 10% DMSO and 20% human serum until the time of surface characterization.

C-mediated lysis. C-mediated lysis was assessed as previously described (33). In brief, 5×10^6 target cells were treated with 0.2 ml ^{51}Cr sodium chromate (292 μCi/ml) (New England Nuclear, Boston, MA) and incubated for 90 min at 37°C. After 2 washes, the cells were diluted to 2×10^5/ml in media containing 10% FCS. Twenty microliters of labeled cells were distributed in conical microtiter plate wells with 20 μl of 10-fold serial dilutions of hybridoma antibody. After a 1-hr incubation at 4°C, 20 μl fresh rabbit serum (1:5 dilution), previously absorbed with 1/10 vol of normal human splenocytes (1 hr, 4°C), were added to the wells as a source of C. After an additional 1-hr incubation at 37°C, 140 μl of media were added to the wells, and the plates were spun at 400 × G for 10 min. One hundred microliters of supernatant were removed from each well and counted on a gamma scintillation counter (Packard Instrumentation Co., Downer's Grove, IL). Specific ^{51}Cr release was calculated by using the following formula:

$$\% \text{ Specific } {}^{51}\text{Cr release} = \frac{Exp - SR}{MR - SR} \times 100\%$$

where Exp = mean of the observed triplicate, SR = spontaneous release from cells incubated with C alone, and MR = maximum release obtained by treating cells with the detergent Triton X (1% solution).

Lysis of larger numbers of cells for subsequent PWM activation experiments was done by resuspending 10×10^6 mononuclear cells in 1 ml of anti-B1 antibody at a 1/100 dilution. After 1-hr incubation at 4°C, 0.25 ml fresh rabbit serum absorbed as above was added, and the cells were incubated at 37°C for an additional 60 min. Cells were then washed 3 times, resuspended in final culture medium (RPMI 1640 containing 20% FCS, 12.5 mM HEPES buffer, 4 mM L-glutamine, and 25 μg/ml gentamycin), and placed into culture.

Antibody absorption and blocking experiments. One hundred microliters of anti-B1 antibody at a 1/1000 dilution were absorbed with 10^8 viable cells from various cell populations including the immunizing Burkitt's tumor cells, E+ (T) cells, sIg+ (B) cells, monocytes, thymocytes, and the cell lines CEM (T) and SB (B). After 1-hr incubation on ice with agitation, absorbing cells were removed by centrifugation for 15 min at 400 × G, and the supernatant was harvested. Residual antibody activity was assessed by indirect immunofluorescence on a B1-positive B cell CLL target cell by methods outlined above. Forty thousand cells were analyzed on the FACS-I. The number of positive cells were enumerated by subtraction of cells staining in the presence of an unreactive monoclonal antibody, and compared with the number staining with unabsorbed anti-B1 antibody. Results were expressed as a percentage inhibition *vs* the control.

Competitive blocking experiments were conducted in order to exclude anti-B1 reactivity with an immunoglobulin determinant. One hundred microliters of anti-B1 at a dilution of 1/1000 were incubated for 1 hr at 4°C with 100 μl of a 1/2 dilution of pooled normal human serum, or 100 μl containing 500 μg of IgM or IgG myeloma protein (Cappel Laboratories, Cochranville, PA), or containing 500 μg of IgD myeloma (kindly provided by Dr. Chester Alpert, Blood Grouping Laboratory, Harvard Medical School, Boston, MA). The specificity of the myeloma protein preparations was confirmed by the selective blocking of heavy-chain specific goat anti-human Ig antisera (anti-IgM, -IgG, and -IgD) (Meloy). After incubation, 100 μl of the mixture were used for indirect immunofluorescence on a B1-positive target cell as outlined above.

Possible anti-B1 reactivity with C3 receptors was examined by attempts to inhibit EAC rosette formation with anti-B1 antibody. B cells (10^6/ml), purified by anti-Fab chromatography, were preincubated with anti-B1 (1/100 to 1/10,000) or an unreactive control ascites for 30 min at 20°C. One hundred microliters of B cells were then reacted with 100 μl of 0.5% EAC 1, 4, 2, 3 (Cordis Laboratories, Miami, FL) for 15 min at 37°C, and centrifuged at 200 × G for 10 min. The cell pellet was resuspended and 50 μl of 0.1% methylene blue were added to facilitate visualization of nucleated cells.

Fc receptor reactivity was assessed by the blocking of binding of anti-B1 to normal B cells or the immunizing Burkitt's tumor cells pretreated with heat-aggregated human IgG (see Reference 43). B cells were either untreated or incubated with aggregated IgG (10 mg/ml) for 1 hr at 20°C, washed twice, and reacted with anti-B1 at dilutions of 1/100 to 1/10,000 for indirect immunofluorescence. The number of cells staining positively in the presence and absence of aggregated IgG were enumerated on the FACS-1.

Cell cultures. Cells obtained after C-mediated lysis of the B1 population or after cell sorting were washed 3 times in tissue culture medium (TCM) and brought to 10^6/ml. One hundred microliters of cells were plated in round-bottom 96-well plates (Linbro Scientific, Hamden, CT), and 100 μl of TCM or TCM containing 50 μg/ml PWM (Difco Laboratories, Detroit, MI) were added to each well. Populations obtained by cell sorting also received 20% E+ (T) cells to facilitate B cell activation by PWM (36, 37). Plates were cultured in 95% air/5% CO_2 humid atmosphere, and cells and supernatants were harvested after 7 days for analysis of differentiation to Ig-secreting cells.

For detection of Ia antigen expression by activated T cells, 10^5 E+ cells were placed in microculture for 7 days in the presence of 5 μg/ml concanavalin A (Con A; Calbiochem, La Jolla, CA). Activated T cells, along with unstimulated control cultures and cryopreserved T cells, were harvested and prepared for immunofluorescent analysis as outlined above.

Reverse hemolytic plaque assay. Ig-secreting cells were enumerated by reverse hemolytic plaque assay as previously described (38). In brief, 50 μl of an 11% suspension of sheep erythrocytes, coated with a polyspecific rabbit anti-human Ig, together with 50 μl of lymphocytes, were pipetted into 10 x 75-mm glass tubes containing 0.9 ml of an 0.8% solution of SeaPlaque agarose (Marine Colloids, Rockland, ME), in Hanks' balanced salt solution (HBSS, Grand Island Biological Co., Grand Island, NY). Tubes were vortexed and layered over 5 ml of gelled 1.0% SeaKem agarose (Marine Colloids) in HBSS in a 60-mm Petri dish. Dishes were incubated for 1 hr at 37°C in a humid atmosphere containing 5% CO_2. One milliliter of rabbit anti-human Ig antiserum diluted 1/100 in HBSS was pipetted onto the dishes, incubated for 1 hr at 37°C, and 1 ml of guinea pig C (GIBCO) diluted 1/10 was added. Incubation was continued for an additional hour and the plaques were enumerated under a dissecting microscope.

Radioimmunoassay for Ig. The production of Ig by PWM-stimulated, fractionated cells was assessed in a solid-phase radioimmunoassay (39). Polyvinyl chloride microtiter plates (Cooke Engineering, Alexandria, VA) were coated with 100 μl of a 1/300 dilution of affinity-purified, polyvalent goat anti-human $F(ab')_2$ antibody in PBS for 2 hr at 4°C. Plates were blocked with 200 μl of 1% bovine serum albumin (BSA) in PBS for 1 hr at room temperature, and washed 3 times with PBS. Twenty-five microliters of culture medium containing various known amounts of human Ig (standards) or 25 μl of culture supernatant were added to each well, followed by 25 μl of ^{125}I-labeled human 7S Ig (Miles-Pentex, Kankakee, IL) containing approximately 8000 cpm. All culture supernatants or standards were tested in triplicate. Plates were gently agitated, covered, and incubated for 16 hr at 4°C. The contents of each well were then aspirated, the plates were washed 5 times in PBS, air-dried, and the wells were excised and counted in a gamma counter (Packard).

Results were calculated by reference to a standard curve generated at the time of each assay. Inhibition was found to be linear over a range of from 3 ng to 200 ng human Ig/25 μl.

RESULTS

Distribution of B1 antigen on normal tissues. For somatic cell hybridizations, BALB/c mice were immunized with tumor cells obtained from a patient with Burkitt's lymphoma. These cells were of B lymphocyte origin as shown by their surface phenotype: IgMκ+, Ia+, Fc+, C3+, E−, OKT3− (anti-T cell) (35), and OKM1− (anti-monocyte) (33).

A monoclonal antibody generated from this fusion, and designated anti-B1, was found, in preliminary screening on the FACS, to react strongly with the immunizing tumor (Fig. 1*A*), and was also present on 9.1 ± 2.0% of the Ficoll-Hypaque fraction of PBM from 13 normal individuals (range: 5.5 to 11.5%). In order to determine the population of cells in normal peripheral blood that bore B1 antigen, mononuclear cells from 7 individuals were separated into T, B, null, and monocyte fractions, stained with anti-B1 and G/M FITC, and analyzed on the FACS. A representative experiment is depicted in Figure 1. As shown, B1 antigen expression was limited to B cells (Fig. 1*B*), but was absent from T cells (Fig. 1*C*), monocytes (Fig. 1*D*), and null cells (not shown, but comparable to Fig. 1*D*). Staining intensity was constant at dilutions of anti-B1 ranging up to 1/2000, diminishing to background levels at 1/50,000.

A quantitative examination of peripheral blood B cells indicated that the number of Ig-positive cells in a B cell preparation

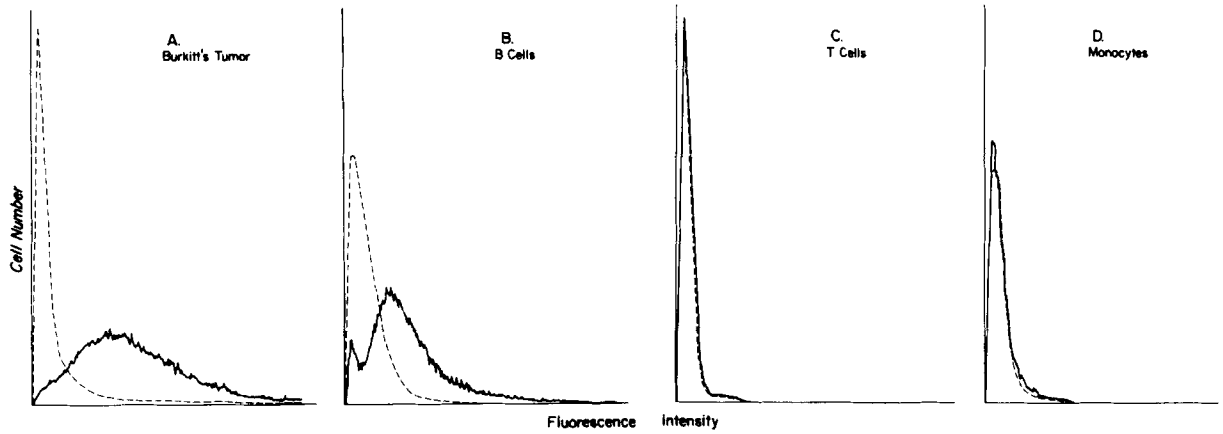

Figure 1. Reactivity of anti-B1 monoclonal antibody on separated peripheral blood mononuclear cells by indirect immunofluorescence: FACS profile. *Broken line*, control ascites, *solid line*, anti-B1. *A*, immunizing Burkitt's lymphoma; *B*, B cells; *C*, T cells; and *D*, monocytes.

was identical with the number of cells staining with anti-B1. In this experiment, cytophilic serum IgG was first removed from anti-F(ab')$_2$ immunoadsorbent-purified B cells by a 1-hr incubation of cells at 37°C (32). B cells were then stained with B1, or a mixed monoclonal anti-κ/anti-λ reagent and G/M FITC, and the number of fluorescent cells was quantitated on the FACS. Approximately 35,000/40,000 cells stained with anti-κ/λ, whereas 34,800/40,000 stained with anti-B1, thus indicating that virtually all B cells in peripheral blood are B1 positive.

A number of normal tissues were also tested for the presence of B1-positive cells. As shown in Figure 2, B1 was found on lymphocytes from tonsil (64%, n = 3), lymph node (36%, n = 5), spleen (35%, n = 3), and a small population of normal bone marrow cells (<5%, n = 3), but was undetectable on thymocytes (n = 3). The intensity of staining with anti-B1 on these other lymphoid tissues was of approximately the same magnitude as found on peripheral blood B lymphocytes.

Reactivity of anti-B1 on cell lines and tumors. The reactivity of anti-B1 was examined on a number of cell lines. All B cell lines (6/6) tested were positive for B1, as were 3/3 Burkitt's lines. Two T cell lines and a line derived from "null" cell ALL (Laz 221) were B1 negative.

Anti-B1 was also tested on a series of circulating tumor cells of lymphoid origin. All B cell tumors tested (18/18) were found to be positive for B1, whereas T cell (0/7) and myeloid tumors (0/2) were B1 negative. B1 thus appears to be limited in expression to malignancies of B cell derivation, and taken together with findings on normal tissues and cell lines, these data strongly suggest that B1 defines an antigen present only on B cells.

Cytotoxicity and absorption studies. C-mediated cytotoxicity and quantitative absorption studies were subsequently undertaken to determine if the specificity of anti-B1 was identical to that found by indirect immunofluorescence. As shown in Table I, B1 was lytic for peripheral blood B cells, but not T cells or monocytes, at dilutions of 1/100 to 1/10,000. Approximately 95% specific lysis was produced on the B cell population, which routinely contained some (5%) contamination by monocytes. Similarly, the B cell lines Laz 156 and Daudi were significantly lysed by exposure to anti-B1 and C at dilutions comparable to those effective on normal cells, whereas no lysis was produced on the T cell lines HSB2 and CEM.

A quantitative absorption experiment was also carried out. Anti-B1 at a dilution of 1/1000 was absorbed with a variety of cells of lymphoid origin, at a final concentration of 10^9 cells/ml antibody. Antibody activity remaining after absorption was assessed by binding to a B cell CLL target cell that had

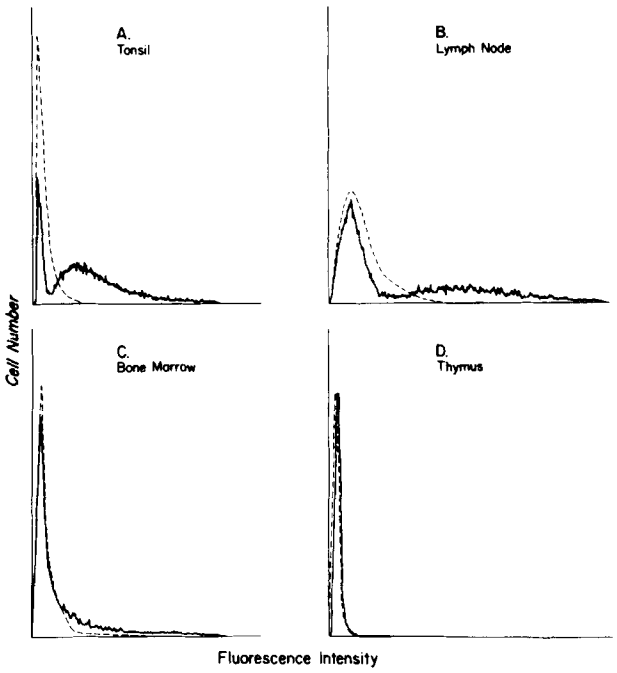

Figure 2. Reactivity of anti-B1 with normal lymphoid tissues. *Broken line*, control ascites; *solid line*, anti-B1. *A*, tonsil; *B*, lymph node; *C*, bone marrow; and *D*, thymus.

previously been found to bear B1. As shown in Table II, B1 activity was significantly removed (>93%) only by B cells, the immunizing tumor, and a B cell line (SB), but not by normal T cells, thymocytes, a T cell line (CEM), or by monocytes (<15%). The small diminution of B1 activity by absorption with the latter cells most probably reflects nonspecific adsorption of antibody, since a similar decrease in activity (approximately 10%) was noted after absorption with mouse spleen cells.

Relationship of B1 to known B cell markers. Blocking experiments were conducted in order to explore the possibility that B1 was an Ig determinant. Anti-B1 antibody at a limiting dilution of 1/2000 was preincubated with an equal volume of pooled human serum (10%) or with several human myeloma protein-rich preparations (5 mg/ml). These mixtures were then added to the appropriate B1-positive target cells (2 B1 positive lymphomas), and the intensity of staining was compared with staining produced by anti-B1 in the absence of inhibitor. Myelomas tested included those of the IgG, IgM, and IgD isotypes. Results are expressed as percent inhibition of cells staining

TABLE I

Cytotoxicity of anti-B1 on cell lines and fractionated lymphocytes

Target Cell	% ^{51}Cr Release at Anti-B1 Dilution:			
	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Laz 156	61.4 ± 3.0	56.0 ± 5.4	54.4 ± 7.2	12.7 ± 5.9
Daudi	68.5 ± 7.2	65.4 ± 2.3	62.4 ± 5.7	34.7 ± 3.0
HSB2	1.3 ± 1.7	0	0.8 ± 1.5	0.9 ± 2.6
CEM	1.0 ± 7.4	2.4 ± 7.4	0	0
Normal B cells	92.2 ± 4.7	99.5 ± 4.2	98.1 ± 4.2	13.7 ± 3.8
T cells	0	0	5.1 ± 6.1	0
Monocytes	5.9 ± 0.9	4.5 ± 0.5	5.7 ± 1.2	2.9 ± 2.1

TABLE II

Quantitative absorption of Anti-B1 antibody

Antibody Treatment	% Absorption[a]
T cells	14.7
B cells	94.5
Monocytes	12.6
CEM	13.8
SB	95.5
Thymus	10.2
Immunizing Burkitt's lymphoma	93.9

[a] % Absorption

$$= 100 - \frac{\text{No. of cells staining above bkgd, absorbed antibody}}{\text{No. of cells staining above bkgd, unabsorbed antibody}}$$

TABLE III

Failure to block B1 reactivity with myeloma proteins or serum immunoglobulin

Antibody	% Inhibition Produced by Preincubation with:			
	Pooled human serum	IgM[a]	IgG[a]	IgD[a]
B1				
Expt. 1[b]	12.3	18.6	0	0
Expt. 2[c]	5.4	2.0	9.1	9.0
Anti-IgM[b]	nd[d]	98.7	0	nd
Anti-IgG[e]	81.9	0	54.5	nd
Anti-IgD[e]	nd	5.9	0	81.0

[a] Final concentration: 2.5 mg/ml.
[b] Tested on immunizing Burkitt's lymphoma.
[c] Tested on B cell D-PDL.
[d] Not determined.
[e] Tested on tonsil.

above background in the presence *vs* absence of inhibitor. The data, presented in Table III, demonstrate that, in several experiments, no Ig-containing serum was capable of significantly inhibiting B1 reactivity. In control experiments, the reactivity of the anti-IgM, anti-IgG, and anti-IgD antisera were reduced to background levels by the corresponding myeloma-rich serum or by pooled normal human serum (Table III). Anti-IgG and anti-IgD reagents were tested on normal tonsillar lymphocytes and anti-IgM was assessed on the immunizing tumor.

Further confirmation that B1 was not an Ig determinant was demonstrated by passage of B1 antibody at a 1/2000 dilution over a human 7S γ-globulin-Sepharose immunoabsorbent column. No decrease in titer was noted by indirect immunofluorescence analysis (data not shown). Furthermore, several B cell-derived malignancies that possessed various combinations of monoclonal surface Ig, including those bearing IgMκ, IgGκ, IgMλ, and IgGλ, were all positive for B1, suggesting that B1 does not recognize an isotype-specific determinant.

The possibility that B1 represents a DR-locus specificity was also considered. Screening studies outlined above showed that adherence-purified monocytes, which are overwhelmingly Ia+ in human blood (13), were completely B1 negative (Fig. 1, Tables I and II), while at the same time reacting strongly with a monoclonal anti-Ia (p29,34) antibody. In addition, indirect immunofluorescent staining of B cells with saturating concentrations (1/100) of anti-B1 and anti-Ia, alone and in combination, always produced additive staining intensity (data not shown). At minimum this result indicates that anti-B1 and anti-Ia define different antigenic determinants. However, since T cells have also been shown to express Ia antigen subsequent to activation by antigen or mitogens (17, 18), experiments were also conducted to examine a possible relationship between Ia and B1 at the T cell level. E-rosette-purified T cells from 5 normal individuals were cultured with and without Con A for 7 days. They were then tested by indirect immunofluorescence on the FACS for the appearance of Ia and/or B1 antigen. As shown in Figure 3, T cells cultured in the presence of media alone were negative for both Ia and B1 (Fig. 3*A*). As anticipated, when T cells were exposed to Con A, approximately 25% developed Ia positivity, indicating their activated state (Fig. 3*B*). However, under these conditions, B1 antigen remained unexpressed (Fig. 3*C*). This experiment therefore provides an additional example of dissociation of Ia and B1 antigen.

Several tumors were also identified that bore large amounts of Ia antigen but were completely B1 negative. These included 2/2 patients with acute myelogenous leukemia and 3/4 patients with non-T non-B (Null cell) acute lymphatic leukemia. Thus, although B1 may represent an Ia antigen that is specific for B cells, it is clearly not present on the same molecule as detected by an anti-Ia antibody directed against an Ia framework determinant.

Finally, studies were conducted in order to demonstrate possible C3 or Fc receptor reactivity with anti-B1. Pretreatment of B cells with varying dilutions of anti-B1 failed to inhibit EAC rosette formation compared with B cells pretreated with an unreactive control ascites (54% EAC and 51% EAC, respectively). Similarly, attempts were made to block anti-B1 reactivity by pretreatment of normal B or the immunizing tumor cells with heat-aggregated human IgG. No diminution in the number of cells staining positively with anti-B1 was noted upon FACS analysis compared with B cells not exposed to aggregated IgG (31,300/40,000 *vs* 30,700/40,000 cells stained).

Determination of the proportion of B cells bearing B1: functional studies. Previous studies have indicated that PWM polyclonally induces the differentiation of B lymphocytes into Ig-secreting plasma cells (40). In order to determine whether all B cells capable of stimulation by PWM also bear B1, PBM

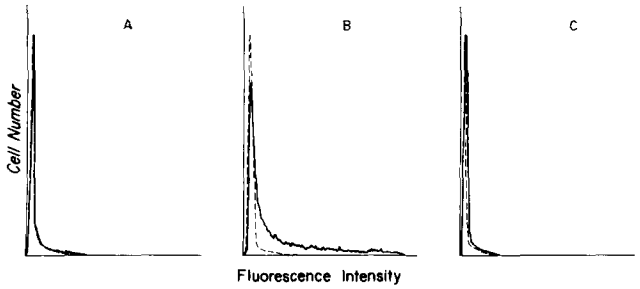

Figure 3. Lack of expression of B1 on activated T cells. *Broken line*, control ascites. *A*, T cells cultured with media; *solid line*, anti-Ia. *B*, T cells cultured with Con A (5 μg/ml); *solid line*, anti-Ia. *C*, T cells cultured with Con A; *solid line*, anti-B1.

were stained with B1 by indirect immunofluorescence and separated into B1-positive and B1-negative fractions by cell sorting. Sorted cells, along with the original, untreated population and a control population, which was stained with anti-B1 and G/M FITC but not sorted, were cultured with and without PWM. Reanalysis of the B1-negative population on the FACS confirmed that all cells staining with B1 or anti-κ/λ had been removed. Because peripheral blood B cell activation by PWM requires T cells (37, 40), 20% E-rosette positive cells were added to all cultures. At the end of 7 days, Ig production was evaluated in a radioimmunoassay (RIA) specific for human Ig. The results, summarized in Table IV, show that Ig was secreted only by unfractionated PBM and by the B1-positive lymphocyte fraction, but not by B1 negative cells, T cells, or monocytes. Ig production in all cases was dependent upon the presence of PWM in the cultures. It was observed that B1-positive cells, which comprised 8% of the unfractionated sample, did not produce proportionately greater amounts of Ig compared with the untreated control. This finding may be the result of inhibition of the response by treatment of the cells with B1 and G/M FITC, since PBM that were stained but not sorted produced a lower response than untreated PBM (220 ng/culture *vs* 950 ng/culture). Two additional experiments produced identical results.

In another approach, unfractionated PBM were treated with anti-B1 and C to determine if any B cells lacked B1 antigen and could therefore escape lysis and go on to differentiate into Ig-secreting cells after PWM stimulation. Control populations were untreated, treated with C alone, or exposed to an unreactive hybridoma antibody and C. A positive control was provided by treatment with the anti-Ia monoclonal antibody and C. All populations were then cultured for 7 days in the presence or absence of PWM. The generation of Ig-secreting cells was assessed both by direct enumeration in a reverse hemolytic plaque assay, and by analysis of culture supernatants by RIA. Three such experiments were carried out and a representative result is presented in Table V. As shown, a significant reverse plaque-forming cell (PFC) response was produced by PWM-stimulated untreated and control populations, all of which gave approximately 5000 PFC/10^6 cultured cells. In contrast, both anti-B1 and anti-Ia treatment totally abrogated the PWM-induced PFC response. Very few PFC were generated in the absence of PWM. Parallel results were obtained when supernatants from these cultures were tested for Ig content by RIA (Table V); once again, both anti-B1 and anti-Ia treated cells failed to produce Ig.

Thus, based on the ability to eliminate totally Ig secretion and reverse PFC, it appears that B1 defines the overwhelming proportion of B lymphocytes capable of PWM-induced differentiation to Ig-secreting cells.

TABLE IV

Pokeweed mitogen activation of B1+ and B1− PBM separated by cell sorting

Cell Population	ng Ig/Culture	
	−PWM	+PWM
PBL[a] (not sorted)	2.1 ± 1	950 ± 30
PBL[a] + anti-B1 (not sorted)	0	220 ± 20
B1+[a]	0	750 ± 150
B1−[a]	0	0
T cells	0	10 ± 15
Monocytes	0	1 ± 15

[a] Twenty percent T cells added.

TABLE V

Pokeweed mitogen-activation of anti-B1-treated PBM

Cell Treatment	PFC/10^6 Cultured Cells		ng Ig/Culture	
	−PWM	+PWM	−PWM	+PWM
None	120 ± 0	5920 ± 800	23 ± 5	510 ± 55
C control	220 ± 120	4620 ± 460	15 ± 1	430 ± 113
Normal ascites + C	140 ± 110	4850 ± 71	19 ± 7	680 ± 98
Anti-B1 + C	90 ± 42	40 ± 28	5 ± 1	0
Anti-Ia + C	30 ± 42	30 ± 14	0	0

DISCUSSION

In the present investigation, we describe a unique human antigen limited in expression to cells of the B lymphocyte compartment. Antigen B1, defined by the use of a monoclonal antibody, was found on approximately 9% of the PBM fraction, >95% of B cells from blood and lymphoid organs, and all tumors and cell lines of B cell lineage. Monocytes, resting and activated T cells, null cells, and tumors of T cell and myeloid derivation were uniformly B1 negative. B1 appeared to be distinct from known phenotypic markers of B cells, including surface Ig and known Ia-like antigens. Of importance, functional studies demonstrated that all cells in human peripheral blood, which can be triggered by PWM to differentiate into Ig-secreting cells, bear B1 antigen.

PWM has been widely employed as a polyclonal B cell activator, which induces the terminal differentiation of B cells to Ig-secreting plasma cells (40). Elimination of the B1+ population with anti-B1 and C or by cell sorting abrogated PWM-stimulated Ig secretion, as determined both by a RIA and a reverse hemolytic plaque technique for detecting individual Ig-secreting cells. Both methods employed a polyvalent anti-Ig antiserum that detects all human Ig isotypes. Taken together with the results from immunofluorescence and cytotoxicity studies that >95% of Ig+ cells are also B1+, it would seem that few B1−B cells could be present. Nevertheless, it remains possible that a small B cell subpopulation, which is both B1− and unstimulatable by PWM, does exist in human peripheral blood. B cell heterogeneity has been observed in the mouse with respect to PWM activation (40), although the behavior of human B cells in this regard is presently unclear. In addition, PWM-induced differentiative responses in human peripheral blood are highly T cell dependent (37, 40), more specifically helper cell dependent (41), and failure of activation may reflect suboptimal T helper influence rather than an inherent functional property of a B cell subpopulation. At the present time we feel that the weight of evidence from both functional and reactivity studies supports the interpretation that most, if not all normal, resting B cells bear B1 antigen.

For the purpose of B cell enumeration B1 possesses the advantage of defining a non-Ig determinant, thus circumventing technical problems related to the binding of serum IgG to cellular Fc receptors (14). Our finding that 9.1% of the peripheral blood mononuclear fraction reacts with anti-B1 is in close agreement with values obtained for integral membrane Ig+ cells obtained after temperature (32) or pH-induced (42) dissociation of cytophilically-bound IgG (8.9% and 9.7%, respectively), or as detected by pepsin-digested anti-Ig reagents (6.3%) (14). B1 should therefore prove to be extremely useful in the isolation and functional analysis of pure B cell populations, as well as in the identification and enumeration of B cells in congenital and acquired immunodeficiency disorders, and in malignancies of B cell derivation.

B1 appears to be distinct from classical B cell phenotypic

markers, particularly Ia antigen and Ig determinants. Antisera with B cell specificity have been previously described, which are in fact directed against Ia-like antigens encoded by the HL-A-D locus (5–8). Such antigens are present on numerous other cell types, including nonlymphoid cells (24), in addition to B lymphocytes. In the present studies, B1 reactivity failed to coincide with that of anti-Ia, in the lack of B1 expression on monocytes and activated T cells (Fig. 1; Tables I and II), and in the identification of a number of tumors that were Ia+, B1−. B1 reactivity could not be inhibited by a variety of human Ig-containing preparations (Table III). Finally, attempts to demonstrate possible Fc or C3 receptor reactivity of anti-B1 were unsuccessful. No inhibition of B1 reactivity was produced by pretreatment of B cells with aggregated human IgG, nor were the number of EAC rosettes in a B cell population reduced by pretreatment of cells with a range of dilutions of anti-B1.

Other B cell-specific antigens have been described, which appear, like B1, to be distinct from Ig and Ia-like antigens on the basis of tissue distribution and/or m.w. (19–23). These include heteroantisera-defined antigens that apparently identify B cell subpopulations (23, 44), as well as antigens with broad B cell representation (20, 22). Further studies are currently in progress in our laboratory to determine the molecular characteristics of B1, its functional relevance, and its possible relationship to other previously described antigens.

Acknowledgments. The authors wish to thank Ms. Lucia Whong and Ms. Joan McDowell for technical assistance, and Ms. Cynthia Raymond for preparation of the manuscript.

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A Unique Cell Surface Antigen Identifying Lymphoid Malignancies of B Cell Origin

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ABSTRACT A monoclonal antibody (anti-B1) specific for a unique B cell surface differentiation antigen was used to characterize the malignant cells from patients with leukemias or lymphomas. All tumor cells from patients with lymphomas or chronic lymphocytic leukemias, bearing either monoclonal κ or λ light chain, expressed the B1 antigen. In contrast, tumor cells from T cell leukemias and lymphomas or acute myeloblastic leukemias were unreactive. Approximately 50% of acute lymphoblastic leukemias (ALL) of non-T origin and 50% of chronic myelocytic leukemia in blast crisis were also anti-B1 reactive. Moreover, 21 of 28 patients with the common ALL antigen (CALLA) positive form of ALL were anti-B1 positive, whereas 0 of 13 patients with CALLA negative ALL were reactive.

These observations demonstrate that an antigen present on normal B cells is expressed on the vast majority of B cell lymphomas and on ~75% of CALLA positive ALL, suggesting that these tumors may share a common B cell lineage.

INTRODUCTION

Leukemias and lymphomas, which were not previously distinguishable by either morphologic or histochemical criteria, can now be subdivided into clinically and pathologically distinct subgroups by use of a number of cell surface markers expressed on normal lymphocytes (1–3). For example, both normal and malignant B cells are defined by their expression of cell surface immunoglobulin (4, 5). Other markers of the B cell membrane, including receptors for the Fc portion of human immunoglobulin (6), receptors for components of the complement system (7), and HLA-D-related Ia-like antigens (8, 9) are less useful because they are not restricted to cells of B lineage and are also found on normal and malignant monocytes (10–12). In addition, Fc receptor-bound immunoglobin may give spuriously positive results for cell surface immunoglobulin (13). Although T cells have been shown to be reactive with anti-T cell antisera (14, 15), or to form erythrocyte rosettes with sheep erythrocytes (16), they, too, may express Fc or C3 receptors or Ia-like antigens (17–19). Finally, Null cells, which lack the conventional markers of T and B cells (20), also have been shown to express C3, Fc, or Ia-like antigens (21–23). Given the extent of overlap of many of these cell surface markers, considerable attention has been directed at defining unique cell surface antigens present on normal T, B, and Null cells, which can then be used to identify and classify leukemias and lymphomas.

In a recent study (24), we described the development and characterization of a monoclonal antibody (anti-B1) that is reactive with a differentiation antigen expressed on all human B cells and on those cells destined to differentiate into immunoglobulin-secreting cells under pokeweed mitogen stimulation. The B1 antigen has been shown to be distinct from other known phenotypic markers of B cells, including surface immunoglobulin, Fc and C3 receptors, and Ia-like antigens. More importantly, anti-B1 was unreactive with normal T lymphocytes, Null cells, and granulocytes. In the present study, we have used anti-B1 to characterize a large number of malignancies thought to be of T, B, monocyte, myeloid, and Null cell origin. These studies demonstrate that anti-B1 reacts only with those B cell lymphomas that express either monoclonal κ or λ light chain. Of considerable interest is the demonstration that tumor cells from the majority of patients with the common acute lymphoblastic leukemia anti-

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Received for publication 4 August 1980 and in revised form 22 September 1980.

gen (CALLA)[1] positive non-T cell form of acute lymphoblastic leukemia (ALL) and chronic myelocytic leukemia (CML) in blast crisis were also reactive with anti-B1 antibody. This study supports the notion that most B cell lymphomas and many CALLA$^+$ ALL share a common B cell lineage.

METHODS

Patients and sample preparations. All patients in this study were evaluated at the Sidney Farber Cancer Institute, the Children's Hospital Medical Center, Peter Bent Brigham Hospital, Beth Israel Hospital, or the Massachusetts General Hospital. The diagnosis of lymphoma or leukemia was made using standard clinical, morphologic, and cytochemical criteria (25–27). Heparinized peripheral blood or bone marrow was collected from leukemic patients or from patients with circulating lymphomas (lymphosarcoma cell leukemias) before the administration of chemotherapeutic agents or blood products. Lymphocytes were separated from these specimens by Ficoll-Hypaque density gradient centrifugation, as previously described (28). Tumor masses and lymphoid tissue from patients with lymphomas were gently teased, minced into single cell suspensions, and passed through stainless steel mesh wire filters. Tumor cells were readily distinguishable from normal lymphocytes by Wright-Giemsa morphology, and all neoplastic preparations selected for this study had >75% abnormal cells. Isolated tumor cells were studied either fresh or cryopreserved in 10% dimethyl sulfoxide and 20% fetal calf serum at −196°C in the vapor phase of liquid nitrogen until the time of surface characterization.

Preparation of normal lymphocyte subpopulations. Human peripheral blood mononuclear cells were isolated from normal volunteer adult donors by Ficoll-Hypaque density gradient centrifugation. Normal lymphoid tissues from tonsil, lymph node, spleen, and thymus were prepared as described above. Unfractionated cells were then separated into B cell (surface immunoglobulin [sIg] positive), T cell (sheep erythrocyte rosette [E] positive), monocyte (adherent), and Null cell (sIg$^-$, E$^-$) by standard techniques (29). In particular, the B cell preparations were routinely >90% sIg$^+$ and <5% E$^+$, nonreactive with anti-T cell antibodies, and ~5% monocytes as judged by morphology, latex ingestion, and reactivity with the monocyte-reactive monoclonal antibody (M1) (30). The T cell populations obtained were <2% sIg$^+$ and >95% E$^+$, uniformly reactive with anti-T cell antibodies, and entirely negative with M1. Normal monocytes were obtained by adherence to plastic dishes as previously described (30), and were 95% M1$^+$, but did not form erythrocyte rosettes, react with anti-T cell antisera, or express sIg. Null cells were sIg$^-$, E$^-$, and T cell antisera negative.

Cell surface markers. The cellular lineage of tumor cells was determined by a number of cell surface markers. The definition of T cell lineage was established by reactivity with a T cell-specific heteroantiserum (14) and monoclonal antibodies (15), and by reactivity with sheep erythrocytes as previously described (16). All the T cell leukemias and lymphomas were >75% reactive with the T cell-specific monoclonal antibodies and heteroantiserum, and these tumor cells were uniformly >20% erythrocyte rosette reactive (31, 32).

The B cell derivation of the tumor cell was demonstrated by the expression of either monoclonal κ or λ light chains on the tumor cell surface. Monoclonal antibodies specific for κ or λ light chain were used in all studies (provided by Dr. Victor Raso, Sidney Farber Cancer Institute, Boston, Mass.). In addition, a monoclonal antibody specific for the framework of the human HLA-D-related Ia-like antigen was used to analyze all normal and malignant cells for reactivity. The Ia-like antigens are gene products of the HLA-D region, which are present on the surface of normal peripheral blood B cells, a fraction of Null cells, monocytes, and activated T cells, but not on resting T cells (33). These Ia-like antigens have not been detected on the vast majority of T cell leukemias and lymphomas, but are expressed on most hematopoietic non-T cell malignancies. The anti-Ia antibody used in this study appears to be identical to the previously described heteroantiserum (19) and monoclonal antibodies (33), which identified a common framework expressed on all Ia-like antigens.

The non-T cell leukemias were characterized using a monoclonal antibody (J-5) (34), which has been shown to have the specificity of a previously described rabbit anti-CALLA antisera prepared in this laboratory (35).

The preparation and characterization of the anti-B1 antibody was the subject of a previous report (24). In brief, anti-B1 was developed by somatic cell hybridization, was cloned by limiting dilution, and has been passaged in ascites form in BALB/c mice for over 1 yr. Ascites form anti-B1 was used for all experiments. This antibody has been shown to be of the IgG_2 subclass and can induce lysis of reactive cells with rabbit complement at dilutions up to 1:50,000. By indirect immunofluorescence, cytotoxicity, and quantitative absorption, the B1 antigen was present on >95% of B cells from blood and lymphoid organs in all individuals tested. Monocytes, resting and activated T cells, Null cells, myeloid cells, and T cell lines were B1 antigen negative. The B1 antigen was shown to be distinct from human immunoglobulin isotypes, Ia-like antigens, Fc receptor of immunoglobulin, and the C3 receptor. Functional studies demonstrated that removal of the B1 antigen positive population from peripheral blood by cell sorting or complement-mediated lysis eliminated the cell population that is induced to differentiate into immunoglobulin-secreting plasma cells by pokeweed mitogen.

Indirect immunofluorescence analysis of normal and malignant cells with monoclonal antibodies. Normal or malignant cells were used fresh or thawed and washed extensively at the time of study; their viability exceeded 85% in all cases. In brief, 1–2 × 10^6 cells were treated with either 0.1 ml of a 1:500 dilution of the specific monoclonal antibody to be tested or 0.1 ml of a 1:500 dilution of an unreactive control antibody of a similar immunoglobulin isotype, incubated at 4°C for 30 min, and washed three times. These cells were reacted with 0.1 ml of a 1:40 dilution of fluorescein-conjugated goat anti-mouse IgG (G/M FITC) (Meloy Laboratories, Inc., Springfield, Va.), incubated at 4°C for 30 min, washed three times, and analyzed as previously described (36). Intensity of fluorescence was determined for 40,000 cells in each population on a fluorescence-activated cell sorter and compared with the fluorescence of a control nonreactive ascites. A displacement of the histogram of the test monoclonal antibody (Fig. 2A) was scored positive compared with the histogram of an unreactive isotype identical monoclonal antibody. In addition, for each test sample, a quantitative assessment of the number of positive cells was made (number of cells reactive with test monoclonal antibody minus number of cells reactive with the unreactive isotype identical monoclonal antibody divided by 40,000 total cells tested). Because the fluores-

[1] *Abbreviations used in this paper*: ALL, acute lymphoblastic leukemia; CALLA, common acute lymphoblastic leukemia antigen; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; E, sheep erythrocyte rosette; G/M FITC, fluorescein-conjugated goat anti-mouse IgG; sIg, surface immunoglobulin.

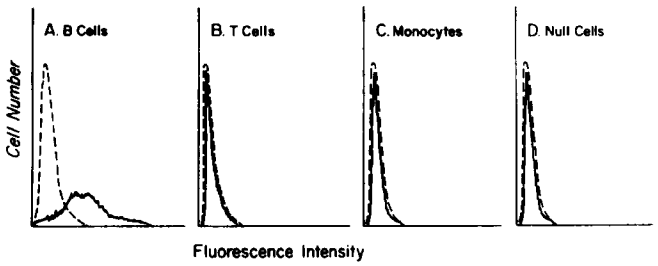

FIGURE 1 The fluorescence profile of fractionated B cells (A), T cells (B), monocytes (C), and Null cells (D) with anti-B1 antibody and G/M FITC (solid line) is depicted in this figure. It is seen that B cells react with the anti-B1 antibody. Background fluorescence staining (dotted line) was obtained by incubating cells with an unreactive monoclonal antibody and developing with G/M FITC.

cence intensity of these antibodies was not different in dilutions from 1:50 to 1:10,000 or greater, it appeared that the intensity of reactivity related to the number of specific antigen-reactive determinants on the cell surface.

RESULTS

Distribution of B1 antigen on normal hematopoietic tissues. As was previously shown (24), anti-B1 identified a surface antigen present on ~9% of unfractionated peripheral blood mononuclear cells. Mononuclear cells from several individuals were separated into T, B, Null, and monocyte fractions and analyzed for reactivity using anti-B1 and G/M FITC. As shown in Fig. 1, the B1 antigen was found uniquely on B cells (Fig. 1A), and was absent from T cells (Fig. 1B), monocytes (Fig. 1C), and Null cells (Fig. 1D). Moreover, the B1 antigen was present on the Ig^+ cells from tonsil (64%; $n = 3$), lymph node (36%; $n = 12$), spleen (35%; $n = 8$), and a small population of normal bone marrow (5%; $n = 5$), but was not detected on thymocytes ($n = 4$). The intensity or amount of reactivity of these tissues with anti-B1 was similar to that found on peripheral blood B cells.

Reactivity of anti-B1 with malignant lymphomas. Anti-B1 was tested for reactivity with the tumor cells from patients with B cell lymphomas. These tumors were determined to be of B cell origin by the presence of cell surface monoclonal κ or λ light chains and by their failure to form erythrocyte rosettes or react with anti-T cell antisera. The tumors were classified according to the scheme of Rappaport (37) and included the following histologic types: (*a*) diffuse, poorly differentiated lymphocytic ($n = 18$); (*b*) diffuse histiocytic ($n = 7$); (*c*) nodular, poorly differentiated lymphocytic ($n = 8$); (*d*) Burkitt's lymphoma ($n = 9$); (*e*) nodular mixed ($n = 3$); (*f*) Waldenstrom's ($n = 2$); and (*g*) myeloma ($n = 3$). In contrast to the patterns obtained with normal B cells, the reactivity of anti-B1 with these B cell tumors varied, and is illustrated in Fig. 2. For example, tumor cells from patients with chronic lymphocytic leukemia (CLL) were weakly but definitively reactive with anti-B1 (Fig. 2A). In contrast, the tumor cells from patients with nodular, poorly differentiated lymphocytic tumors (Fig. 2B) were moderately reactive, whereas the tumor cells from patients with Burkitt's lymphoma were strongly reactive (Fig. 2C). Of considerable interest was the finding that all plasma cell myelomas tested were unreactive (Fig. 2D). The results obtained with cells of 50 patients with B cell lymphoma are summarized in Table I. The tumor cells from all 47 patients with classical B cell lymphoma were reactive with anti-B1, anti-Ia, and either anti-κ or anti-λ light chain, but not both. The three plasma cell myelomas tested were unreactive with anti-B1. The tumor cells from two of these patients lacked both the Ia antigen and surface κ or λ; however, the tumor cells from the third patient expressed both. In contrast, only one of three patients with Null cell lymphoma was $B1^+$, although the tumor cells from all three of these patients were reactive with an anti-Ia antisera. Moreover, all 13

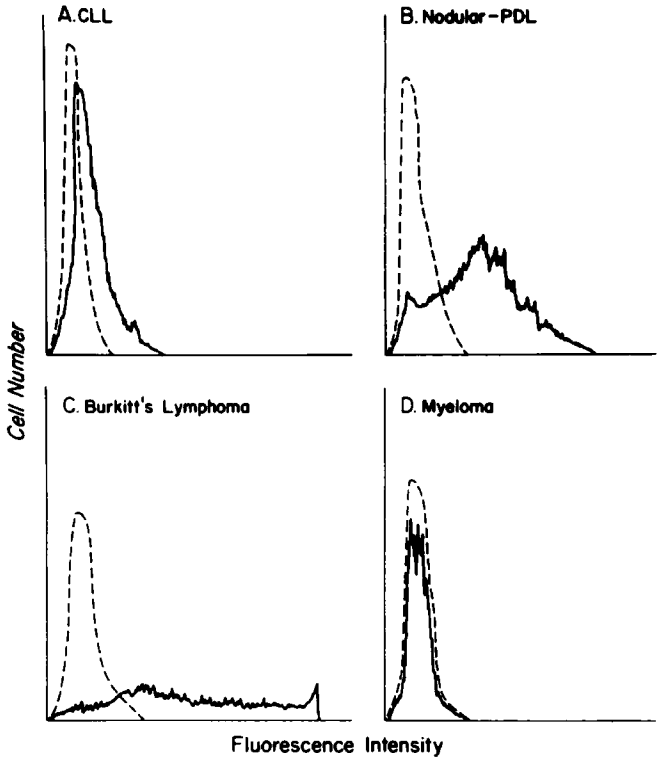

FIGURE 2 The fluorescence profile of tumor cells from patients with B cell CLL (A), nodular, poorly differentiated lymphocytic lymphoma (B), Burkitt's lymphoma (C), and plasma cell myeloma (D) with anti-B1 antibody and G/M FITC (solid line) is depicted in this figure. It can be seen that tumor cells from patients with CLL are weakly reactive, nodular, poorly differentiated lymphocytic cells are moderately reactive, Burkitt's lymphoma strongly reactive, and plasma cell myelomas are unreactive with anti-B1. Background fluorescence staining was performed as in Fig. 1.

TABLE I
Reactivity of Lymphomas and Leukemias with Anti-B1

Tumor	Number of patients	Number reactive with antisera			
		Ia	B1	κ or λ	Anti-T cell
Lymphomas					
B cell	50	48	47	48	0
Null cell	3	3	1	0	0
T cell	13	0	0	0	13
Leukemias					
CLL	18	18	18	18	0
ALL—non-T	41	41	21	0	0
ALL—T cell	17	0	0	0	17
CML—stable phase	6	4	0	0	0
CML—blast crisis	10	7	5	0	0
AML*	16	15	0	0	0

* AML, acute myeloblastic leukemia.

T cell lymphomas tested were unreactive with anti-Ia, anti-B1 and anti-κ or anti-λ monoclonal antibodies.

Reactivity of anti-B1 with leukemias. Since the vast majority of sIg-bearing (B cell) lymphomas were reactive with anti-B1, we next evaluated the expression of the B1 antigen on leukemic cells. As can be seen in Table I, the tumor cells from patients with CLL expressed monoclonal surface κ or λ light chain, Ia antigen, and B1 antigen. An unexpected result was noted when the ALL cells were tested with anti-B1. It was found that the tumor cells from ~50% of the patients with non-T cell ALL were $B1^+$. Leukemic cells from these individuals lacked surface κ or λ, but were $B1^+$ and Ia^+. T cell ALL were unreactive with anti-B1 and anti-Ia. In contrast, tumor cells from patients with acute myeloblastic leukemia were generally Ia^+ and uniformly lacked the B1 antigen. These findings provided additional support for the view that the anti-B1 was unreactive with conventional sIg or Ia-like antigens. In addition, it was found that 5 of 10 patients with CML in blast crisis were $B1^+$, whereas 0 of 6 patients with stable phase CML were unreactive with anti-B1.

Coexpression of B1 antigen and CALLA on non-T cell leukemias. Given the reactivity of anti-B1 with some, but not all, non-T cell ALL, the relationship of the B1 antigen to CALLA was then investigated. Previous studies have shown that CALLA is a tumor-associated antigen expressed on the leukemic cells from 80% of

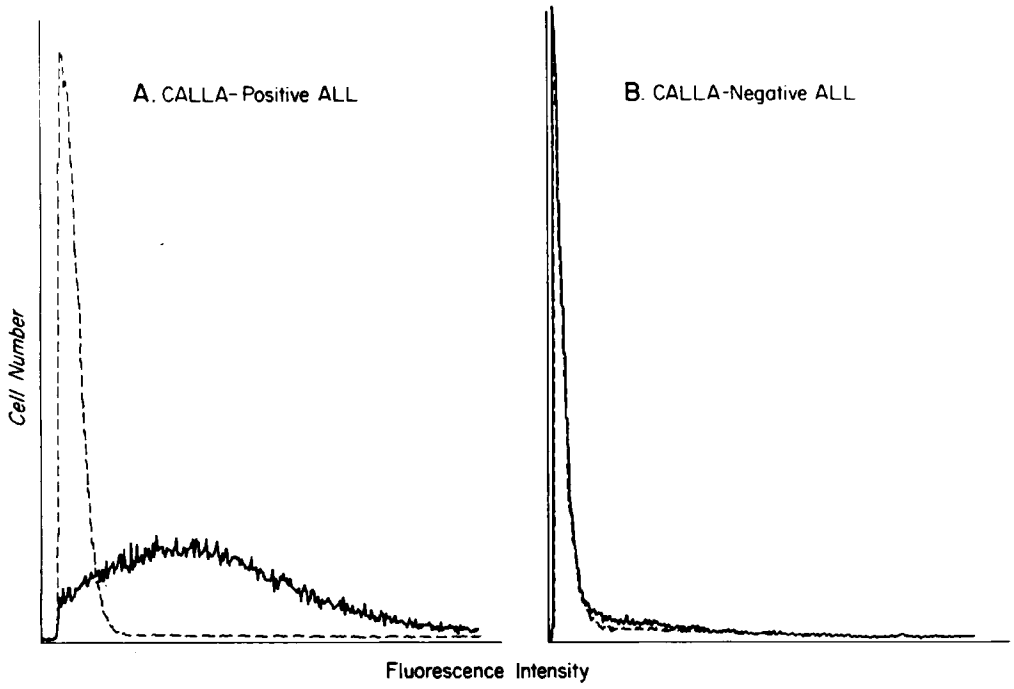

FIGURE 3 The fluorescence profile of the tumor cells from a patient with a $CALLA^+$ ALL (A) and $CALLA^-$ ALL (B) with anti-B1 antibody and G/M FITC (solid line) is depicted in this figure. It can be seen that the tumor cells from the $CALLA^+$ ALL were uniformly reactive with anti-B1 (A), whereas the tumor cells from the $CALLA^-$ patient were unreactive (B). Background fluorescence staining was performed as in Fig. 1. The tumor cells from approximately one-third of patients with $CALLA^+$ ALL had an identical fluorescence pattern to the one depicted in Fig. 3A. The fluorescence intensity patterns of the two-thirds of patients with $CALLA^+$ ALL were equally divided between weak expression (similar to Fig. 2A) and moderate expression (similar to Fig. 2B).

TABLE II
Reactivity of Anti-B1 with CALLA Positive and Negative Leukemic Cells

Tumor	Number of patients	Number reactive with antisera	
		Ia	B1
Non-T cell ALL, CALLA$^+$	28	28	21
Non-T cell ALL, CALLA$^-$	13	13	0
CML—blast crisis, CALLA$^+$	7	6	5
CML—blast crisis, CALLA$^-$	3	1	0

patients with non-T cell ALL and ~30% of patients with CML in blast crisis (38). This antigen has been shown to be a glycoprotein with a molecular mass of 100,000 daltons. Recently, a monoclonal antibody (J-5), specific for CALLA, has been described. The tumor cells from 41 patients with non-T ALL and 10 patients with CML in blast crisis were then compared for their reactivity with anti-Ia, anti-CALLA, and anti-B1 monoclonal antibodies. The reactivity of anti-B1 with the tumor cells from a CALLA positive and a CALLA negative patient is depicted in Fig. 3. Fig. 3A shows that the tumor cells from a patient with CALLA$^+$ ALL were reactive with the anti-B1 antibody, whereas Fig. 3B shows that the tumor cells from a patient with CALLA$^-$ ALL were unreactive. Further heterogeneity of the CALLA$^+$ ALL and CML in blast crisis could be demonstrated by their reactivity with anti-B1. As shown in Table II, the tumor cells from 21 of 28 patients with CALLA$^+$, Ia$^+$ ALL were reactive with anti-B1. In contrast, no tumor cells from the 13 patients with CALLA$^-$, Ia$^+$ ALL were reactive. Similarly, most of the CALLA$^+$, Ia$^+$ CML in blast crisis were anti-B1 reactive; and all of the CALLA$^-$, Ia$^+$ CML in blast crisis were unreactive.

DISCUSSION

In the present study, we have used a monoclonal antibody previously shown to be specific for a B cell surface-differentiation antigen to characterize malignant cells from patients with leukemias and lymphomas of various cellular origins. Examinations of the non-Hodgkin's lymphomas with classical cell surface markers demonstrated that ~80% of these tumors and >95% of CLL are of B cell lineage (3). Morphologically, the B cell lymphomas are heterogeneous, and the observed histologic diversity has led to the development of several classification schemes (37–40). These B cell tumors have also been shown to be variable in their amount of expression of surface or intracytoplasmic immunoglobulin, complement receptors, formation of monkey erythrocyte rosettes, Fc receptors, and Ia-like antigens. It has therefore been postulated that the cell surface marker and histologic diversity seen in these tumors may reflect distinct stages of B cell differentiation in which the malignant cells are "frozen" (41). Unfortunately, the various cell surface markers presently used define neither unique histologic subtypes nor distinct clinical subgroups. Nevertheless, given the better prognosis of B cell neoplasms compared with T or Null cell tumors, a number of these markers have been widely used (42, 43).

In this study, the tumor cells from all 18 patients with B cell CLL and 47 of 50 patients with B lymphomas, all bearing κ or λ light chains, were reactive with the anti-B1 antibody. Moreover, anti-B1 was unreactive with acute T cell leukemias and lymphomas and with tumor cells from all patients with acute myeloblastic leukemia. These observations suggest that anti-B1 adds to the repertoire of cell surface determinants that define B cell tumors, and unlike Ia, Fc, and C3, it is restricted to this class of cells. More importantly, the presence of B1 antigen in conjunction with the expression of monoclonal κ or λ light chains provides additional criteria for the definition of a malignant B cell clone. In this regard, normal B cells and other cells capable of binding immunoglobulin via an Fc receptor are invariably heterogeneous with regard to their light chain phenotype, and as such, can be distinguished from B cell neoplasms.

Although anti-B1 was reactive with the vast majority of B cell lymphomas and all B cell CLL, the non-T cell ALL were divided into several distinct entities. These tumor cells have been shown to be unreactive with anti-T and anti-Ig reagents, but to be strongly reactive with anti-Ia and anti-CALLA. Previous studies have shown that 95% of non-T cell ALL are Ia$^+$, whereas CALLA was coexpressed on ~80% of the non-T cell ALL. These studies indicated that the majority of non-T cell ALL were CALLA$^+$, Ia$^+$, and a small group were CALLA$^-$, Ia$^+$. Little is known about the small subset of patients (1–2%) who express cell surface immunoglobulin and are therefore thought to represent a more mature B cell ALL.

The present studies have shown that the tumor cells from ~50% of patients with non-T cell ALL were reactive with anti-B1. More importantly, most of the CALLA$^+$, Ia$^+$ ALL were anti-B1 reactive, whereas all of the CALLA$^-$, Ia$^+$ ALL were anti-B1 unreactive. Thus, the non-T cell ALL can now be divided into three major subclasses: (*a*) CALLA$^+$, Ia$^+$, B1$^+$; (*b*) CALLA$^+$, Ia$^+$, B1$^-$; and (*c*) CALLA$^-$, Ia$^+$, B1$^-$. These studies provide additional support for the view that a significant fraction of CALLA$^+$ ALL was B cell derived. Other investigators have demonstrated that ~20–30% of CALLA$^+$ ALL had the characteristics of pre-B cells in that they contained intracytoplasmic μ chain and lacked both surface and cytoplasmic light chains (44–46). The present study would suggest that, in fact, the majority

of CALLA$^+$, Ia$^+$ ALL are B cell derived, since 75% were anti-B1$^+$. Whether B1 is expressed earlier than cytoplasmic immunoglobulin in B cell differentiation, or is a more sensitive marker of pre-B cells, is yet to be resolved.

The demonstration that the B1 antigen is expressed on all normal B cells, B cell lymphomas, and a proportion of acute leukemias suggests that the B1 antigen is expressed on most stages of B cell differentiation. It was intriguing to find that the generally accepted end-stage cell in B cell ontogeny, the plasma cell, lacked B1. Thus, B1 appears to be a B cell differentiation antigen present throughout most stages of B cell maturation. Similarly, a number of anti-T cell antibodies have been described that are capable of dissecting normal intra- and extrathymic maturation (47), as well as defining distinct subsets of clinically relevant malignant T cell leukemias and lymphomas (31, 32, 38, 48, 49).

Because monoclonal antibodies are of extremely high titer and can be produced in unlimited quantities compared with heteroantisera, the utility of this marker can now be readily adopted by many laboratories studying B cell tumors. Additional B cell-specific antibodies will be required for the dissection of distinct stages of B cell differentiation and for the identification of clinically relevant subgroups of B cell lymphoproliferative malignancies.

ACKNOWLEDGMENTS

The authors would like to thank the members of the Divisions of Hematology, Oncology, Pathology, and Surgery of the Sidney Farber Cancer Institute, the Peter Bent Brigham Hospital, the Beth Israel Hospital, the Children's Hospital Medical Center, and the Massachusetts General Hospital for help in obtaining tissue specimens. We would also like to thank Dr. Alan C. Aisenberg for his encouragement and helpful discussions. We would also like to thank Mr. John Daley for technical assistance, and Ms. Luci M. Grappi for excellent secretarial assistance during the preparation of this manuscript.

This work was supported by National Institutes of Health grants AI 12069, CA 19589, CA 06516, RR 05526, and DE 04881.

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J Immunol. 1987 Nov 15;139(10):3521-6.

Production of a mouse-human chimeric monoclonal antibody to CD20 with potent Fc-dependent biologic activity.

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Mouse monoclonal antibody 2H7 recognizes the CD20 cell surface phosphoprotein that is expressed in normal as well as malignant B cells. CD20 may be a useful target for therapy of B cell lymphomas, since damaged normal B cells can be replaced by their antigen-negative precursors. Monoclonal antibody 2H7 is an IgG2b (kappa) immunoglobulin which cannot mediate antibody-dependent cellular cytotoxicity with human lymphocytes or complement-dependent cytotoxicity with human serum. We have now generated a chimeric 2H7 antibody by substituting the mouse constant domains of 2H7 with the human gamma 1 and kappa domains. This new antibody has the same binding specificities as 2H7 but is highly effective in mediating antibody-dependent cellular cytotoxicity with human effector cells and complement-dependent cytotoxicity with human complement.

PMID: 3119711 [PubMed - indexed for MEDLINE]

American Journal of Pathology, Vol. 139, No. 4, October 1991

Rapid Communication

Expression of B-cell Antigens by Hodgkin's and Reed–Sternberg Cells

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Twenty frozen and 55 paraffin sections of lymph-node specimens from 55 patients with pretreatment Hodgkin's disease (nodular sclerosis Hodgkin's disease, n = 45; mixed cellularity Hodgkin's disease, n = 10) were studied by immunohistochemistry and molecular analysis to determine the phenotype of Hodgkin's and Reed–Sternberg cells (HRS). In all cases the HRS cells were CD45−, and CD30+, and in 43/55 (78%) cases they were CD15+. In 48/55 cases (87%) HRS cells were reactive with at least one B-cell marker (CD19, CD20, CD22, CDw75, MB2), 8/55 cases (14.5%) showed reactivity (mainly cytoplasmic) of a subpopulation of HRS cells with the T-cell markers CD3 and βF1. All cases that expressed T-cell antigens were also reactive with at least one B-cell marker. In frozen sections, a minority of HRS cells in each case studied showed cytoplasmic positivity for bcl-2 protein. Rearrangement of immunoglobulin heavy chain genes was detected in one case and of T-cell receptor β chain genes in none. The authors were unable to confirm previous reports of bcl-2 gene rearrangement in Hodgkin's disease. The results strongly support a B lymphocytic origin of HRS cells. (Am J Pathol 1991, 139:701–707)

Despite numerous studies on the histogenesis of Hodgkin and Reed–Sternberg (HRS) cells, their nature still remains enigmatic. Using a wide variety of approaches derivation has been suggested from macrophages,[1–6] interdigitating reticulum cells,[7–9] activated lymphocytes,[10] immature lymphoid cells,[11] B cells[12–19] and T cells.[20–25]

Immunohistochemical and molecular genetic evidence is accumulating that HRS cells are derived from either B or T lymphocytes rather than macrophages and interdigitating reticulum cells with most immunohistochemical studies favoring a T-cell derivation of these cells.[20–25] Most of these studies favoring a T-cell derivation of HRS cells have, however, used a limited panel of mono- or polyclonal antibodies specific for B and T cells and in some instances have used T-cell markers alone.[22,24]

In contrast to immunohistochemistry most molecular studies[13,14,17,26–28] have pointed towards a B-cell phenotype of HRS cells. Furthermore, the recent report of bcl-2 gene rearrangement in a significant number of Hodgkin's disease cases,[19] if confirmed, would be strong evidence in this direction.

We report the results of a combined immunohistochemical and molecular study of 55 cases of Hodgkin's disease (excluding the lymphocyte predominant subtype). We have used a broad panel of antibodies against both B and T cells performed genotypic analysis by Southern blotting and have attempted to confirm the presence of bcl-2 gene rearrangement as reported by Stetler–Stevenson et al.[19]

Material and Methods

Immunohistochemistry

Seventy-five specimens from 55 patients with pretreatment Hodgkin's disease (55 paraffin sections, 20 frozen sections) were taken from the surgical pathology files of the Department of Pathology, University College and Middlesex School of Medicine, London, and stained with

Supported by the Cancer Research Campaign and the North East Thames Regional Health Authority. Christine Schmid is a visiting fellow from the Institute of Pathology, University of Graz, Austria, and is a recipient of a Schrödinger–Stipendium/Fonds zur Förderung der wissenschaftlichen Forschung, Austria.

Accepted for publication July 12, 1991.

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the panel of monoclonal and polyclonal antibodies listed in Table 1. The alkaline phosphatase anti–alkaline-phosphatase (APAAP) method[29] and a modification of the ABC method[30] were used for frozen and paraffin sections, respectively. Paraffin sections were predigested with trypsin (Sigma) when using the antibodies CD15, CD30, CD3 (polyclonal), and βF1. Each specimen was classified according to the Rye classification as either nodular sclerosis Hodgkin's disease (NSHD) (n = 45) or mixed cellularity HD (MCHD) (n = 10). Nodular lymphocyte predominant Hodgkin's disease (NLPHD) was not included in this study. The percentage of cells staining with antibodies specific for B and T cells was estimated as less than 10, 10–50, and over 50. Attention was given to ensure that the immunoreactive HRS cells were unequivocally tumour cells, especially in cases where less than 10% of HRS cells expressed the respective antigens (e.g., the presence of characteristic nuclear details and surrounding T-cell rosettes). All cases were examined separately by two of the authors (CS, PGI). The distribution of staining, i.e., cytoplasmic, surface or both was also noted.

Molecular Genetics

Gene Rearrangement Analysis

High molecular weight DNA was extracted from 18 frozen biopsy specimens of HD as described previously.[31] The purified DNA was digested separately with three restriction enzymes (EcoR1, HindIII, PstI). The resulting digests were size-fractionated on 0.8% agarose gels and transferred to Hybond N-plus membranes (Amersham, UK) by Southern blotting. The recombinant DNA probes used included those encoding the J_H region of the immunoglobulin (Ig) heavy chain[32] and the constant region of the β chain of the T-cell receptor (TCRβ).[33] They were radiolabelled with 32 P-dCTP by the random hexamer method.[34] After the hybridization, the membranes were washed under stringent conditions and exposed to prefogged X-ray film at −70°C.

Polymerase Chain Reaction (PCR)

Fresh frozen tissue of 19 specimens and paraffin material from 32 cases (all of the paraffin sections showing reactivity of HRS cells with CD20) were studied using PCR.[35] Two sets of PCR were carried out for each sample: one using primers designed to amplify the major breakpoint region of t(14;18),[36] the other using primers designed to amplify a fragment of the normal β-globin gene,[35] as a control. Forty-five cycles of PCR were carried out on a thermal cycler (Hybaid, UK) using a mixture of 1 unit of Taq polymerase, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 10 mM MgCl, 0.001% gelatine, 200 μM each dNTP, 200 ng of DNA or one dewaxed paraffin section, and 250 ng of DNA primers (obtained from Oswell DNA Service, Edinburgh, UK). PCR products were visualized on an ethidium bromide stained 3% agarose gel and analyzed by conventional Southern blotting,[31] using a radiolabelled probe to the bcl-2 major breakpoint (pFL3).[37] A follicular lymphoma with known bcl-2 major breakpoint rearrangement was used as positive control. Extracted placental DNA and dewaxed sections of reactive tonsillar tissue were used as positive controls for the β-globin amplification and as negative controls for the major breakpoint amplification.

Results

Immunohistochemistry

The results obtained with antibodies specific for B- and T-cells in 20 frozen sections are listed in Table 2. In all

Table 1. *Details of Antibodies Employed and Their Source*

CD-antigen	Antibody	P/F	Source	Ig class	Major lymphoid specificity
CD19	HD37	F	1	Ig G1	B cells
CD20	L26	P/F	1	Ig G2a	B cells
CD22	4KB128	F	2	Ig G1	B cells
CDw75	LN1	P	3	Ig M	B cells
—	MB2	P	4	IG G1	B cells
CD3	UCHT1	F	5	Ig G1	Peripheral T cells
CD3	CD3 (poly)	P	1	—	Peripheral T cells
—	βF1	P/F	6	Ig G1	β chain of T cell receptor
—	bcl-2 protein	F	2	Ig G	B cells, T cells
CD15	Dako M1	P	1	Ig Mκ	HRS cells
CD30	BerH2	P	1	Ig G1	Ki-1 activation antigen
CD45RB	PD7/26—2B11	P	1	Ig G1	Leukocyte common antigen

P = paraffin sections; F = frozen sections; 1 = DAKO; 2 = Dr D. Y. Mason, Oxford, UK; 3 = ICN, Biomedicals; 4 = Eurodiagnostics; 5 = Prof. P. Beverley, ICRF, London, UK; 6 = Laboratory Impex Limited, London.

Table 2. *Immunophenotype of HRS Cells: Frozen Sections**

ST	n	%	CD19	CD20	CD22	CD3	βF1
NS	14	>50	0	1	2	0	0
		10–50	6	5	3	2	1
		<10	4	6	3	2	2
		(0)	(4)	(2)	(6)	(10)	(11)
MC	6	>50	2	1	0	0	0
		10–50	3	3	3	0	0
		<10	0	2	1	1	0
		(0)	(1)	(0)	(2)	(5)	(6)
TO	20		15 (75%)	18 (80%)	12 (60%)	5 (25%)	3 (15%)

* Staining patterns: CD19, CD20: surface; CD22: cytoplasmic; CD3: cytoplasmic (1 case surface); βF1: cytoplasmic (1 case membrane).
ST = subtype; n = number of cases; % = percentage of immunoreactive HRS cells; NS = NSHD; MC = MCHD; TO = Total.

cases HRS cells expressed at least one B-cell antigen (Figure 1a–c) with all three B-cell antigens being expressed in 50% of cases and two in a further 25%. CD19 and CD20 expression was seen on the surface of various numbers of HRS cells, whereas CD22 expression was confined to the cytoplasm as is appropriate for B cells in other than mature stages of differentiation.[38] As can be seen from Table 2, in most cases less than 50% of HRS cells were reactive with the B-cell markers. T-cell antigens were expressed by a minority of HRS cells in only 5 (25%) cases (Figure 1d) and in only one of these were the antigens expressed appropriately (i.e., on the cell surface/membrane). In two of these five cases, the HRS cells also expressed all three B-cell antigens, with expression of two in a further two cases and a single B-cell antigen in one case. In each frozen section, a minority of HRS cells showed moderate-to-strong cytoplasmic reactivity for bcl-2 protein.

In paraffin sections a variable number of HRS cells in each case were reactive with CD30. In 43/55 (78%) of cases CD15 positive HRS cells were identified. Using CD30 and CD15 HRS cells displayed membrane staining and/or a cytoplasmic paranuclear dotlike reactivity. No reactivity of HRS cells was observed with CD45

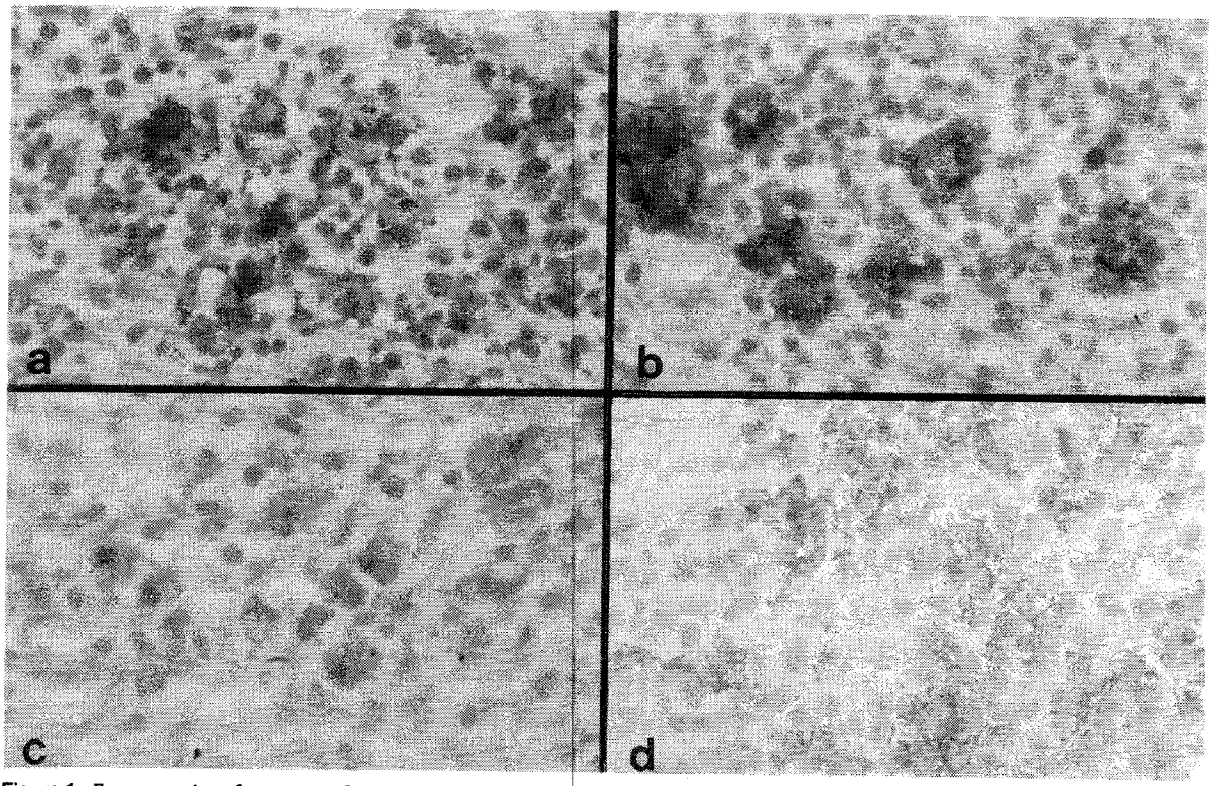

Figure 1. *Frozen sections from cases of Hodgkin's disease stained* (a) *with CD19,* (b) *with CD20,* (c) *with CD22 and* (d) *with CD3. There is strong surface membrane staining of HRS cells with the B cell markers CD19 and CD20 while CD22 stains the cytoplasm. CD3 staining is confined to the cytoplasm (immunoalkaline phosphatase).*

Table 3. *Immunophenotype of HRS Cells: Paraffin Sections**

ST	n	%	CD20	CDw75	MB2	CD3	βF1
NS	45	>50	11	5	1	0	0
		10–50	4	8	4	1	0
		<10	10	9	7	4	0
		(0)	(20)	(23)	(33)	(40)	(45)
MC	10	>50	0	1	0	0	0
		10–50	5	3	5	0	0
		<10	2	4	1	0	0
		(0)	(3)	(2)	(4)	(10)	(10)
TO	55		32 (58%)	30 (55%)	18 (33%)	5 (9%)	0

* Staining patterns: CD20: surface; CDw75: surface and/or cytoplasmic; MB2, CD3: cytoplasmic.
ST = subtype; n = number of cases; % = percentage of immunoreactive HRS cells; NS = NSHD; MC = MCHD; TO = Total.

(CD30, CD15 and CD45 were not applied on frozen sections). Using antibodies to B and T cells in paraffin sections (Table 3) HRS cells expressed at least one B-cell antigen in 42/55 (76.4%) cases (Figure 2a, b, c). In 32 (58%) of these, HRS cells strongly expressed the B-cell specific antigen CD20 whereas in the remaining 10 cases they expressed B–cell-associated antigens recognized by the antibodies CDw75 or MB2. Again, as in frozen sections less than 50% of HRS cells were reactive with B-cell markers in most of the cases. Weak-to-moderate expression of CD3 antigen (Figure 2d) was detected in the cytoplasm of occasional (a single cell in two cases) HRS cells in five cases in all of which the cells expressed at least one B-cell antigen. None of the HRS cells in paraffin sections were reactive with βF1.

Molecular Genetics

Of 18 cases of HD analyzed by Southern blotting only one (NSHD) showed rearrangement of the Ig heavy chain gene which was present in DNA digested with each of the three restriction enzymes. Using the polymerase chain reaction (PCR), no rearrangement of the bcl-2 gene (major breakpoint) was detected in any of the 19 frozen and 32 paraffin cases.

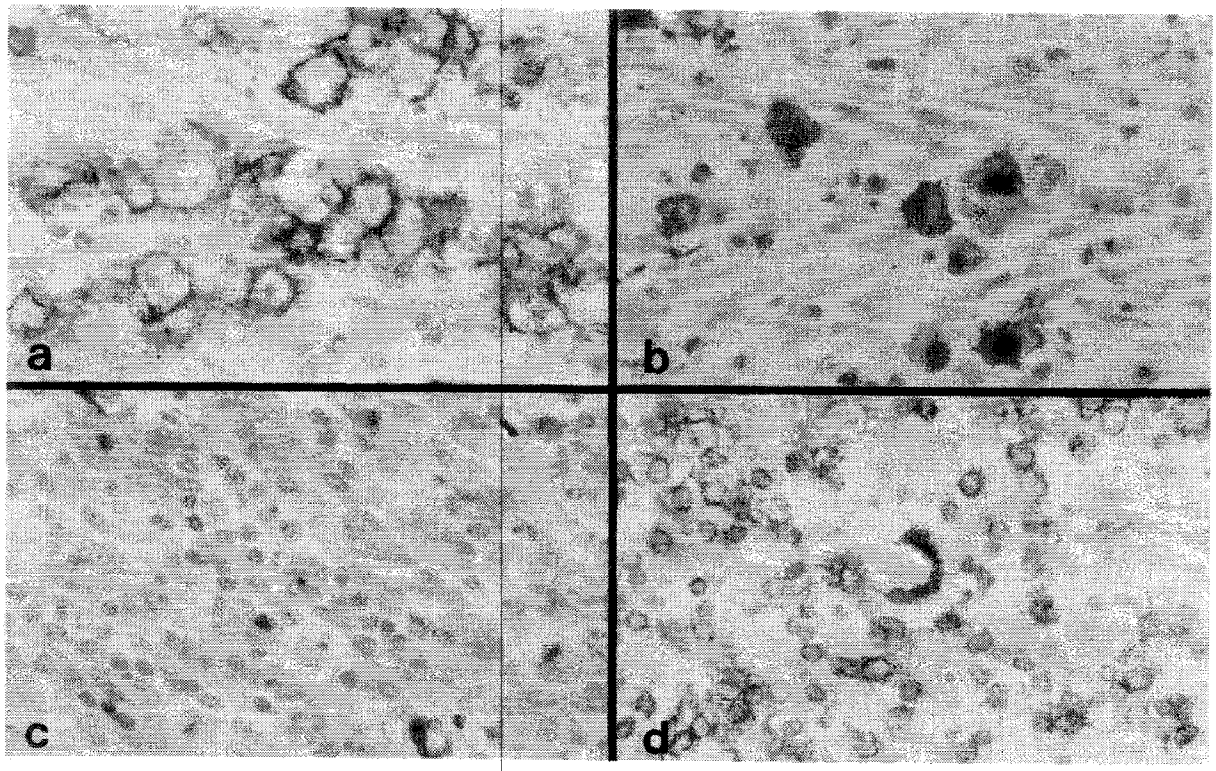

Figure 2. *Paraffin sections from cases of Hodgkin's disease stained* (a) *with CD20,* (b) *with CDw75,* (c) *with MB2 and* (d) *with CD3. The B-cell markers CD20, CDw75, and MB2 clearly label HRS cells. CD3 staining is confined to the cytoplasm of HRS cells in contrast to surface membrane labelling of surrounding T lymphocytes (immunoperoxidase).*

Discussion

Following the work of Stein et al.,[10] who described the constant expression by HRS cells of the lymphoid activation antigen CD30, there has been a broad consensus that these cells are derived from lymphocytes. Opinions are, however, divided as to whether HRS cells are derived from B cells, T cells, or both. Most immunohistochemical studies have favored a T-cell origin.[20,22–25] Many of these immunohistochemical studies are flawed in respect of the small number of cases studied,[20,23] a failure to include B-cell markers,[22,24] or to report their results obtained with B-cell markers.[25] Furthermore, the suggested T-cell origin of HRS cells in immunohistochemical investigations is mainly based on descriptions of intracytoplasmic, rather than appropriate membrane expression, of T-cell markers such as CD3.[11,20,24] Although cytoplasmic CD3 expression does not completely exclude a T-phenotype, cytoplasmic CD3 expression, as far as we are aware, has not been described in T-cell lymphomas. Strong evidence that aberrant cytoplasmic CD3 expression can occur in B cells is provided by Cibull et al.[24] who reported CD3 expression in RS (presumably the L & H variant) cells in three cases of nodular lymphocytic predominant HD. A B-cell phenotype of the L & H variant RS cells in this disease is well recognized[39] and Cibull et al.[24] argue for the aberrant nature of CD3 staining in their cases. In this respect, we have observed positive cytoplasmic staining with CD3 in at least 30% of the cells in three B-cell lymphoblastic cell lines, whereas the B-cell markers used in our study did not stain any cells in five T-lymphoblastic cell lines (unpublished observations). Molecular genetic investigations of Hodgkin's disease, although compromised by the small numbers of tumor cells present in the tissue, have tended to favor a B-cell derivation of HRS cells.[13,14,17,26–28] When selected cases of HD were used (either with high content of RS cells, or following HRS cell enrichment by cell separation techniques, Ig gene rearrangement could be detected in a higher percentage of cases.[13,14,40] Recent descriptions of the integration of Epstein–Barr virus (EBV) in HRS cells[41–46] provide further evidence in favor of a B-cell origin although in rare instances EBV has been reported to occur in T-cell lymphomas.[47,48] In addition, the frequent association of Hodgkin's disease with B-cell non-Hodgkin's lymphoma[49–51] in contrast to only occasional reports of HD with associated T-cell lymphomas[51,52] implies a relation between Hodgkin's disease and B cells.

Our immunohistochemical findings provide evidence in support of a B-cell origin of HRS cells. However, in most cases, a minority of HRS cells expressed B-cell antigens, which is different from non-Hodgkin's B-cell lymphomas in which almost all the tumor cells express B-cell markers. This finding was also observed in the study of Pinkus et al.,[53] who found a variable number of L26 (CD20) positive HRS cells in 34/63 (54%) of their investigated cases. Using the antibody L26, which recognizes the CD20 antigen in frozen and paraffin-embedded tissue,[54] membrane staining of HRS cells was detected in 76.4% of our cases overall and in 90% of cases in which frozen sections could be studied. Not surprizingly, this indicates a degree of antigen loss resulting from tissue fixation and processing. Antibody L26, which was not used in most of the previous immunohistochemical studies of Hodgkin's disease, is a particularly avid B-cell specific reagent in both frozen and fixed tissue.[16] If the other B-cell restricted markers, CD19 and CD22, are included, in 80% of our cases HRS cells show an unequivocal B-cell phenotype. If the results with the B-cell associated markers MB2 and CDw75 are included, in 87% of our cases of Hodgkin's disease the HRS cells showed a B-cell phenotype. Our results using T-cell markers are comparable to those of other workers showing cytoplasmic reactivity with T-cell markers in a minority of HRS cells.[11,20,24] Significantly in each case in which T-cell markers were positive B-cell antigens were also expressed.

With the Southern-blotting technique, we were able to determine a B-cell genotype in only one case of Hodgkin's disease (NSHD). This may reflect insufficient sensitivity of Southern blotting when the neoplastic population accounts for only a minority of cells in the tissue and is common to all previous studies of Hodgkin's disease using this technique.[11,17,26–28] Alternatively, the paucity of evidence of Ig gene rearrangement in Hodgkin's disease may reflect the role of EBV in its pathogenesis, for which there is increasing evidence.[42,44–46] With rare exceptions,[47,48] EBV selectively infects B-lymphocytes and in EBV-induced B-lymphoblastic cell lines, the cells, while continuing to express B-cell surface antigens, often do not show evidence of rearranged Ig genes.[55] Lack of sensitivity cannot explain our inability to confirm the findings of Stetler–Stevenson et al.[19] who demonstrated bcl-2 gene rearrangement in Hodgkin's disease with PCR. Said et al. were likewise unable to confirm these findings but these authors used a slightly less sensitive method.[28] Our PCR method is of similar sensitivity to that used by Stetler–Stevenson et al., and we have no explanation for this discrepancy. Bcl-2 protein expression in malignant lymphomas, which was present in only a minority of HRS cells in each of our cases, has been shown not to be dependent on the presence of a t(14;18) translocation.[56,57] Although we did not find differences in levels of bcl-2 expression in HRS cells compared with surrounding small lymphocytes, such differences might be seen in paraffin material or cytocentrifuged cell preparations, since differences in staining

intensity have been observed in tumor cells of follicular non-Hodgkin's lymphomas.[56] There is a high Ki-67 score in HRS cells in Hodgkin's disease,[20,58] and bcl-2 expression in only occasional HRS cells may be explained by the failure of those cells in cycle to express the protein.[57]

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Japanese Journal of Clinical Oncology

- Oxford Journals
- Japanese Journal of Clinical Oncology
- Volume 13, Number 3
- Pp. 477-488

Japanese Journal of Clinical Oncology 13:477-488 (1983)

Monoclonal Antibody Studies in B(Non-T)-Cell Malignancies

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Tumor cells suspensions prepared from 129 B- or non-T cell malignancies were investigated with a panel of 10 monoclonal antibodies and conventional surface marker techniques. Surface immunoglobulin (slg) and Bl antigen proved to be the most useful markers for B-cell lineage. Six major subtypes of acute lymphoblastic leukemia (ALL) of non-T cell nature are now recognized by these immunological techniques, including null-ALL, Ia-ALL, lymphoid stem cell ALL, pre-pre-B ALL, pre-B ALL and B-ALL.

In cases of chronic leukemias and lymphomas of non-T cell nature, 80% of the tumor was defined by slg and 88% by Bl antigen as definitely of B-cell lineage. The clonal character was also defined in 68% of the tumor on the basis of the detection of predominant single light chain in slg. Ia-like antigen was detected in almost all cases (96%).

Leukemic cells from all cases of chronic lymphocytic leukemia (CLL), chronic lymphosarcoma cell leukemia (CLsCL) and hairy cell leukemia (HCL) reacted with OKIal and anti-Bl, and leukemic cells from most of them with anti-pan T monoclonal antibody (10.2). In more than half of CLL and CLsCL, leukemic cells were reactive with J5, OKM1, 9.6 and OKT8, but not with OKT3, OKT4 and OKT6. HCL cells had almost the same reactivity with these monoclonal antibodies as CLL and CLsCL cells except that J5 remained unreactive. These results indicated that Japanese CLL, CLsCL and HCL were different from Western ones at least with respect to surface marker characteristics.

In cases of lymphomas, heavy chains of sIg were expressed in polyclonal fashion, especially in follicular lymphoma and diffuse lymphomas of medium sized cell type and large cell type, indicating that lymphomas of these types may originate from follicular center cells of the heavy chain switching stage. Anti-T monoclonals were also reactive with lymphoma cells. In about half of follicular lymphomas and diffuse lymphomas of the medium sized cell type, lymphoma cells reacted with 10.2, and less frequently with 9.6, OKT4 and OKT3. On the other hand, only in one or two cases of diffuse lymphoma of the large cell type and of immunoblastic sarcoma (IBS), did tumor cells react with 10.2 and 9.6, but this was exceptional. In more than 25% of IBS, tumor cells also reacted with OKT8, but not with 0KT4 and OKT3. These results indicated that anti-T monoclonals are no longer specific for T-cell lineage. It must be recognized that, in B- or non-T cell lymphoma as well as chronic leukemia, tumor cells are sometimes reactive with several anti-T monoclonals. These results can cause confusion. Therefore, it is still necessary to perform conventional marker studies in addition to monoclonal antibody studies in the case of B- or non-T cell malignancies. Further development of useful anti-B monoclonals is strongly desired.

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Monoclonal Antibody 1F5 (Anti-CD20) Serotherapy of Human B Cell Lymphomas

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Four patients with refractory malignant B cell lymphomas were treated with continuous intravenous (IV) infusions of murine monoclonal antibody (MoAb) 1F5 (anti-CD20) over five to ten days. Dose-dependent levels of free serum 1F5 were detected in all patients. Two patients had circulating tumor cells and in both cases 90% of malignant cells were eliminated from the blood stream within four hours of initiation of serotherapy. Antigenic modulation did not occur, and sustained reduction of circulating tumor cells was observed throughout the duration of the infusions. Serial bone marrow aspirations and lymph node biopsies were examined by immunoperoxidase and immunofluorescence techniques to ascertain MoAb penetration into extravascular sites. High doses (100 to 800 mg/m^2/d and high serum 1F5 levels (13 to 190 μg/mL) were required to coat tumor cells in these compartments in contrast to the low doses that were adequate for depletion of circulating cells. Clinical response appeared to correlate with dose of MoAb administered with progressive disease (52 mg), stable disease (104 mg), minor response (1,032 mg), and partial response (2,380 mg) observed in consecutive patients. The patient treated with the highest 1F5 dose achieved a 90% reduction in evaluable lymph node disease, but the duration of this remission was brief (six weeks). This study demonstrates that high doses of 1F5 can be administered to patients with negligible toxicity by continuous infusion and that clinical responses can be obtained in patients given >1 g of unmodified antibody over a ten-day period.

MONOCLONAL ANTIBODY (MoAb) serotherapy of malignancy represents a theoretically attractive, potentially nontoxic approach for the treatment of neoplastic disease.[1-3] Preliminary animal experimentation has demonstrated both the effectiveness and limitations of MoAbs that recognize tumor-associated antigens in preventing growth of murine hematologic malignancies.[4,5] Early human trials have shown that infusion of antibodies recognizing lymphoid cell differentiation antigens is a well-tolerated therapy capable of coating tumor cells and causing tumor regression in some patients.[6-8] However, the antitumor effectiveness of MoAbs has been limited by the presence of circulating free antigen, antigenic modulation, development of human antimouse antibodies (HAMA), emergence of antigen-negative tumor cell variants, and the inadequacy of host effector cell mechanisms.[5,8-11]

Here we present findings in four patients with B cell lymphomas treated with a murine IgG2a MoAb (1F5) chosen to avoid many of the previously encountered obstacles. MoAb 1F5 recognizes a 35,000 dalton antigen (Bp35, CD20) present on the surface of normal and malignant B cells[12] that is not shed from the cell surface (unpublished observations), does not modulate in response to MoAb binding, and does not bind to any other normal tissues. Consequently, prolonged continuous MoAb 1F5 therapy can be administered without inducing the unresponsiveness to therapy that has necessitated intermittent bolus therapy in previous trials.[8-11] We have administered 1F5 by continuous intravenous (IV) infusion (52 to 2,380 mg over five to ten days) to determine toxicity, kinetics, penetration to extravascular tissues, and efficacy. Our studies have shown 1F5 to be a minimally toxic therapy capable of depleting circulating tumor cells at low doses and lymph node tumor cells at high doses. However, responses were transient, suggesting that antibodies conjugated to toxins or radioisotopes might afford more lasting clinical benefit than unmodified antibody.

MATERIALS AND METHODS

Antibody preparation. Murine MoAb 1F5 (IgG2a) was produced in BALB/c mice and purified as previously described.[13] Antibody 1F5, along with the B1 antibody,[15] has been assigned to the CD20 (anti-Bp35) cluster group by the Second International Workshop on Human Leukocyte Differentiation Antigens.[14] The reactivity of antibody 1F5 with normal and malignant B cells has previously been reported.[13,16,17] MoAb 1F5 was purified from ascites by saturated ammonium sulfate precipitation followed by diethyl aminoethyl (DEAE)-Sephacyl (Pharmacia, Piscataway, NJ) column chromatography.[16] Testing of the purified antibody by Microbiological Associates (Bethesda, MD) has shown it to be free of bacterial, viral, or endotoxin contamination. Preclinical testing in two macaques (*M. fascicularis*) injected with 1F5 IV showed that this antibody was capable of eliminating circulating B cells and penetrating lymph nodes without causing any acute toxicity (J. Ledbetter, unpublished observations, 1983). A battery of normal human autopsy tissues was screened for reactivity with antibody 1F5 by an indirect immunoperoxidase method. No reactivity was seen with any tissue except those known to be rich in B lymphocytes (tonsils, lymph nodes, spleen). Tissues failing to bind 1F5 included heart, thyroid, adrenal, lung, muscle, kidney, testis, skin, colon, breast, and brain.

Patient selection. Adult patients with histologically confirmed B cell lymphomas shown by immunoperoxidase or immunofluorescence techniques to be reactive with the 1F5 antibody were eligible

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Submitted April 17, 1986; accepted September 11, 1986.

Supported by grants AG-04360 from the National Cancer Institute, A120432 from the National Institutes of Health, and by Institutional Cancer Grant IN-26Z from the American Cancer Society. Dr Oliver W. Press is the recipient of a Career Development Award (#85-35) from the American Cancer Society and Dr E. Donnall Thomas is the recipient of a Research Career Award (A102425) from the National Institute of Allergy and Infectious Diseases.

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0006-4971/87/6902-0032$3.00/0

for this study if they had failed previous conventional therapy (chemotherapy and/or radiotherapy), if they had normal renal and hepatic function (creatinine <2.0 mg/dL, bilirubin <1.5 mg/dL), had evaluable disease, had not received any other treatment for ≥four weeks, had no other active medical problems, and signed an informed consent approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Study design. Prestudy blood, marrow, and lymph node specimens were obtained and analyzed by conventional histopathology and by an indirect immunoperoxidase method (Vectastain, Vector Laboratories, Raritan, NJ) for evidence of tissue involvement with tumor cells capable of binding 1F5. Cell suspensions of these tissues were analyzed by two-color flow cytometry using a panel of fluorescein and phycoerythrin antibody conjugates[13] to determine the baseline immunologic phenotypes of the resident cell populations (see below). Intradermal skin testing with 10 μg of antibody 1F5 in 0.1 mL of normal saline was performed, and no hypersensitivity responses were observed. Allopurinol (300 mg/d) was given throughout antibody administration. A bolus loading dose was given over one to two hours IV to rapidly achieve steady state serum antibody levels. The loading dose was calculated from the following equation: Loading dose = 1.4 × elimination half-time (in days) × daily maintenance dose.[18] Preclinical studies of murine anti-CD20 antibody infusions in nonhuman primates (Ledbetter, unpublished data) and clinical trials of murine MoAbs administered to patients with graft-ν-host disease (GVHD)[19] suggested an elimination half-time of 1.2 days, and this figure was used in calculating the loading doses. Patients were assigned a predetermined maintenance antibody dose that was diluted in 500 mL normal saline and administered by continuous IV infusion for five to ten days. (Patient 1 had premature discontinuation of his infusion after five days due to rapidly progressive lymphoma.) The maintenance antibody doses administered to the patients are summarized in Table 1. The dose escalation range was chosen to progress from safe low doses (5 mg/m²/d) known to be well tolerated for other MoAbs[6,7,9,10,19] to high doses (400 to 800 mg/m²/d), which we felt were more likely to result in good tissue penetration. We initially planned to escalate doses between patients. However, because of the absence of toxicity, poor penetration of low doses of antibody into patients 1 and 2, and slow patient accrual, doses were escalated progressively in patients 3 and 4 (from 10 mg/m²/d to 800 mg/m²/d) to achieve high circulating antibody levels that we felt would be more likely to achieve extravascular tissue penetration.

Table 1. Summary of Patient Characteristics

Patient	1	2	3	4
Age/Sex	42/M	64/M	63/M	45/M
Type of Lymphoma	DML	WDLL	DPDL	DHL
Stage	IVB	IVA	IVA	IVB
Total Dose of IF5	52.4 mg	104.8 mg	1,032 mg	2,380 mg
Duration of Therapy	4.5 days	10 days	10 days	7 days
Response	Progression	Stable Disease	Minor Response	Partial Response

Abbreviations: DML, diffuse mixed small and large cell lymphoma; WDLL, diffuse well-differentiated lymphocytic lymphoma (small lymphocytic, working formulation); DPDL, diffuse, poorly differentiated lymphocytic lymphoma (diffuse small cleaved cell, working formulation); DHL, diffuse "histiocytic" lymphoma (diffuse large cell lymphoma, working formulation).

Patient monitoring. Pretreatment tests included a history and physical examination, relevant radiographic studies and computed tomographic scans, chemistry batteries, uric acid levels, complete blood cell counts (CBCs) and differentials, prothrombin time, partial thromboplastin time, serum complement levels (CH50, C4, C3), immune complex levels (C1Q binding assay), urinalysis, ECG, and cell surface marker analysis. Patients were examined twice daily during antibody infusion. Serial serum specimens for 1F5 levels and antimouse antibody levels, blood counts, chemistries, and blood specimens for surface marker studies were obtained four hours after initiation of 1F5 therapy and daily thereafter. Patients were discharged at the termination of antibody infusions. Blood samples were obtained on an outpatient basis for the above tests on days 1, 2, 7, and 21 after cessation of therapy and monthly thereafter. Serum complement and immunoglobulin levels were tested pretreatment and on days 1, 5, and 10 and then at roughly monthly intervals for six months.

Response criteria. Standard response criteria were employed as follows: Complete response-disappearance of all measurable and evaluable disease; Partial response; reduction by ≥50% of leukemic cell counts and ≥50% reduction in the size of a measurable lesion, and no increase in the size of any measurable or evaluable lesions or appearance of new lesions; Stable disease: Less than a partial response without an increase of >25% in leukemic cell count and <25% increase in any measurable lesion. Progression: Increase in leukemic cell count (>25%), appearance of new lesions, or an increase of 25% or greater in any measurable lesion.

Measurement of free 1F5 and human antimouse antibody. Serum 1F5 levels and human antimouse antibody levels (HAMA) were measured by solid phase competitive inhibition radioimmunoassay (RIA) as previously described.[19]

Detection of cell-bound 1F5. Assessment of tumor cell coating by infused antibody 1F5 was accomplished on serial specimens of peripheral blood, bone marrow, and lymph nodes by indirect immunoperoxidase and immunofluorescence techniques. Peripheral blood and bone marrow mononuclear cells were obtained by Ficoll-Hypaque (LSM, Litton Bionetics, Kensington, MD) density gradient centrifugation. Lymph node biopsies were divided in thirds: one portion was minced into a single cell suspension, another part was fixed in formalin for routine histologic staining, and another portion was frozen in liquid nitrogen for immunohistologic staining. Lymph node frozen sections were fixed to gelatin-coated glass slides and stained with rabbit antimouse immunoglobulin (Vectastain, Vector Laboratories, Raritan, NJ) using an indirect avidin-biotin technique. Pretreatment biopsies served as controls.

Cell suspensions of blood, bone marrow, and lymph nodes from antibody-treated patients were examined by flow cytometry (FACS IV, Becton Dickinson, Sunnyvale, CA) for the presence of surface 1F5 by using fluorescein-conjugated goat antimouse immunoglobulin (FITC-GAMIg; TAGO, Burlingame, CA). The mean fluorescence intensity of cells stained with FITC-GAMIg was compared to the intensity of cells incubated with excess 1F5 in vitro before staining to assess the saturation of binding sites in vivo. Relative CD20 surface antigen density was estimated for normal and malignant B cells by measuring the mean fluorescence intensity of cells stained in vitro with saturating quantities of fluorescein-conjugated anti-CD20 antibody after correcting for nonspecific fluorescence with a control reagent.[13,17]

Tumor cell surface antigen phenotypes were determined by both immunofluorescence and immunoperoxidase methods using peroxidase, fluorescein, or phycoerythrin conjugates of MoAbs 10.2 (anti-CD5), HB10a (anti-DR), G1–4 or 3E10 (antikappa), and 2C3 (anti-μ) as previously described.[13,17] Serial monitoring of these tumor cell markers demonstrated that CD20-negative tumor cells were not

generated during 1F5 therapy by antigenic modulation (data not shown).

CASE HISTORIES

Patient 1 was a 42-year-old man with stage IVB diffuse, mixed, small and large cell lymphoma who presented in 1982 with fever, diffuse lymphadenopathy, and hepatosplenomegaly. Previous therapy included CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy, intrathecal methotrexate, whole brain irradiation, splenectomy, sequential upper and lower hemibody irradiation, and four cycles of bleomycin, cytosine arabinoside, vincristine, procarbazine, and prednisone. He was referred for 1F5 therapy in July, 1984 because of refractory disease. He did not respond to low-dose 1F5 and was taken off study after five days of infusion because of progressive bone marrow (BM) and liver replacement with tumor. Salvage CHOP chemotherapy was given, but the patient died of progressive lymphoma on March 16, 1985.

Patient 2 is a 64-year-old man with stage IVA diffuse, small, lymphocytic lymphoma diagnosed by lymph node (LN) and BM biopsy in 1976. He received multiple chemotherapeutic regimens (CVP, CHOP, chlorambucil, and CCNU, etoposide, and methotrexate) with partial responses. He was referred for 1F5 serotherapy in December 1984, 11 months after his last course of chemotherapy. He did not respond to low dose 1F5 but had stable disease that did not require therapy until the summer of 1985 when he was begun on bleomycin, etoposide, BCNU, and Decadron, to which he remains partially responsive.

Patient 3 was a 63-year-old man with stage IVA diffuse, small, cleaved-cell lymphoma involving lymph nodes, marrow, and spleen. Previous therapy included splenectomy, chlorambucil, and CVP. He was referred for 1F5 therapy in December 1984, one month after his last cycle of CVP because of the development of refractory disease with rapidly progressive adenopathy and lymphocytosis (>30,000 cells/μL). He showed a minor response to intermediate dose 1F5 therapy. ProMACE/MOPP chemotherapy was given in January and February 1985 without response. A partial response occurred after therapy with high-dose cytosine arabinoside, but the patient died with marrow aplasia in July 1985.

Patient 4 was a 45-year-old man with sclerosing, diffuse large-cell lymphoma presenting in January 1983 with bowel and lymph node involvement. Therapy included eight cycles of CHOP, intrathecal methotrexate, involved field abdominal radiation, prophylactic cranial irradiation, and allogeneic marrow transplantation (in March 1984). He was referred for 1F5 therapy because of refractory lymphoma in late October 1985. He had been on dexamethasone (4 mg/d) for many months as symptomatic therapy for myalgias, and this was continued during serotherapy. After treatment with 1F5 there was a partial response that lasted six weeks. He then redeveloped progressive lymphoma and refused further treatment. He expired on December 21, 1985.

RESULTS

Serum 1F5 levels. Circulating free antibody levels were detectable by RIA in all patients throughout the period of infusion (Fig 1). Patients 1 and 2 received MoAb doses of 5 mg/m^2/d and consistently had 1F5 serum concentrations of 0.3 to 1.0 μg/mL. Patients 3 and 4 received escalating antibody doses and had corresponding increases in 1F5 levels. For comparable antibody doses the patients with circulating antigen-positive tumor cells (1 and 3) had lower serum levels of 1F5 than the patients who did not have significant numbers of circulating malignant lymphocytes (2 and 4, see Fig 1), probably reflecting the effect of antibody

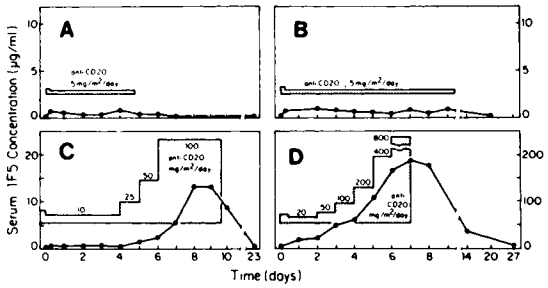

Fig 1. Serum 1F5 concentrations in patients receiving continuous infusions of antibody. MoAb 1F5 concentrations were determined by solid phase radioimmunoassay. The doses of 1F5 infused in each patient are indicated by the superimposed stippled bars. (A), patient 1; (B), patient 2; (C), patient 3; (D), patient 4.

binding to tumor cells. Antibody remained detectable in the serum for as long as three weeks after termination of infusion in patient 4 (peak concentration 190 μg/mL). However, 1F5 levels fell into the undetectable range within three days of termination of infusion in patients 1 and 2 (peak levels 1 μg/mL) and within two weeks in patient 3 (peak level 13.4 μg/mL). Rough estimates of the serum elimination half-times were calculated to be 24 hours for patient 1 (from 0.93 μg/mL to .22 μg/mL in the 48 hours after termination of infusion), 42 hours for patient 3 (from 13.4 μg/mL to 9.0 μg/mL in 24 hours), and 52 hours in patient 4 (from 179 to 35.6 μg/mL over five days). Data for patient 2 were insufficient for estimation of a serum half-life. These elimination half-times are in good agreement with previous studies of murine anti-CD20 antibodies in nonhuman primates (J. Ledbetter, unpublished results) and studies of murine anti-T cell antibodies in patients with GVHD.[19]

CD20 antigen density on tumor cells. Table 2 summarizes the relative Bp35 surface antigen densities on patient lymphoid cells from blood, bone marrow, and lymph nodes as determined by direct immunofluorescent analysis.[13,17] The density of this antigen on normal B lymphocyte populations is also listed for comparison. Patients 1 and 4 had CD20 densities on their malignant cells comparable to those seen on normal, resting B lymphocytes (eg, peripheral blood B cells and tonsil mantle zone B cells[13]). Patient 3 had a much higher surface antigen density on his lymphoma cells, comparable to that observed on normal, activated B cells (tonsil germinal center cells[13]). Patient 2 had a very low Bp35 antigen density on his lymph node and bone marrow tumor cells with a mean fluorescence intensity only 3.5 times higher than control cell populations lacking the antigen. (This degree of staining was unequivocally greater than control, however.) Patients 2 and 4 had negligible numbers of circulating tumor cells morphologically, confirming the negligible staining with FITC-1F5 seen by immunofluorescence (nearly all circulating lymphocytes were T cells in these patients). Of interest, the bone marrow of patient 4 was grossly involved with tumor but failed to bind FITC-1F5, suggesting that an antigen-negative tumor cell variant was responsible for infiltration of this tissue. With this single exception, the different sites of lymphomatous involvement within a given patient showed similar CD20 antigen densi-

Table 2. Relative CD20 Antigen Densities on Normal and Malignant Lymphoid Cells

Cell Type	Relative Antigen Density*
Normal Tissues	
1. Peripheral Blood T cells	2†
2. Peripheral Blood B cells	82
3. Tonsil Mantle Zone B cells	70
4. Tonsil Germinal Center B cells	256
Lymphoma Patients	
1. Patient 1‡	
a. Blood lymphocytes	96
2. Patient 2	
a. Bone marrow	7
b. Lymph node cells	7
3. Patient 3	
a. Blood lymphocytes	301
b. Bone marrow cells	301
c. Lymph node cells	235
4. Patient 4	
a. Blood lymphocytes (uninvolved)	2
b. Bone marrow cells	2
c. Lymph node cells	84

*Expressed as the linear channel number of the mean fluorescence intensity measured on a FACS IV cell sorter for cells stained with saturating concentrations of fluorescein-conjugated anti-CD20 antibody by the method of Ledbetter and Clark.[13]

†Negative control (unstained) cells also showed a mean fluorescence intensity of 2.

‡Patient 1 had an unaspirable marrow and no accessible adenopathy, so immunofluorescent studies were done solely on circulating malignant cells.

ties. No definitive conclusion regarding the clinical responsiveness of tumors bearing different surface CD20 densities is possible because of the small number of patients treated and variable antibody doses administered.

Effects of 1F5 on peripheral blood lymphocytes. Two patients (1 and 3) had appreciable numbers of circulating malignant cells. In both patients antibody administration resulted in an immediate decrease in the number of circulating tumor cells (assessed by morphological criteria and by surface immunologic phenotypes). Patient 1 had an 86% decline in the number of blood lymphoma cells (from 1.27 × $10^3/\mu L$ to 0.18 × $10^3/\mu L$) within four hours of institution of 1F5 therapy. Patient 3 had a 91% decrement in circulating tumor cells (from 18.21 × $10^3/\mu L$ to 1.61 × $10^3/\mu L$) in the same brief time interval (Fig 2). These effects were obtained with low doses of antibody in both patients (5 mg/m^2 and 10 mg/m^2, respectively) and were sustained throughout the entire period of infusion (five and ten days). Flow cytometry of circulating PBL stained with FITC-GAMIg demonstrated saturation of 1F5 antibody binding sites on tumor cells in both patients (although complete saturation in patient 3 was only achieved at the higher dose of 100 mg/m^2/d, Fig 3). Serial tumor cell surface-antigen phenotyping (using two-color immunofluorescence with reagents recognizing other tumor-associated antigens [see Materials and Methods]) demonstrated that antigenic modulation did not occur (data not shown). In both patients termination of 1F5 therapy was accompanied by a rapid reappearance of

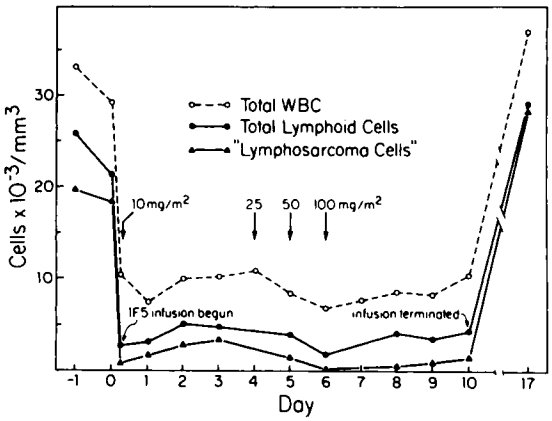

Fig 2. Depletion of circulating lymphoma cells in patient 3 during infusion of MoAb 1F5.

circulating tumor cells that reached pretreatment levels within two to three days (Fig 2).

Effects of 1F5 on bone marrow tumor cells. Patients 1, 2, and 3 had evaluable marrow involvement with lymphoma. In patients 1 and 2, antibody doses of 5 mg/m^2/d were not sufficient for saturation of 1F5 antibody binding sites on tumor cells in the marrow. Patient 3 received escalating doses of 1F5 in conjunction with serial marrow aspirations to estimate the amount of antibody required for coating of tumor cells in the marrow. Serial fluorescence histograms (Fig 4) clearly showed that an antibody dose of 10 mg/m^2/d was insufficient (4% saturation of Bp35 binding sites) but that 100 mg/m^2/d could produce significant coating (61% saturation of Bp35 binding sites) of marrow tumor cells.

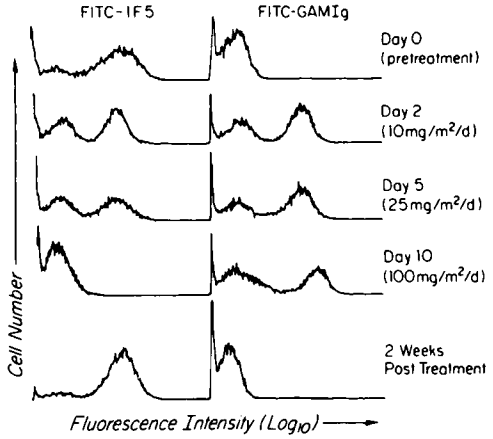

Fig 3. In vivo labeling of circulating tumor cells with 1F5 antibody in patient 3 as assessed by serial flow cytometry of peripheral blood lymphocytes with FITC-GAMIg (to detect mouse antibody 1F5 bound to tumor cells in vivo) and FITC-1F5 (to detect unoccupied Bp35 [CD20] binding sites). Pretreatment PBL stained brightly with FITC-1F5 because of abundant free CD20 sites on circulating lymphoma cells. Serial histograms on days 2, 5, and 10 revealed coating of PBL with 1F5 (detected with FITC-GAMIg). Saturation of binding sites is shown on day 10 by absence of unoccupied Bp35 receptors capable of binding FITC-1F5. By two weeks posttreatment, bound murine MoAb was no longer detectable on PBL.

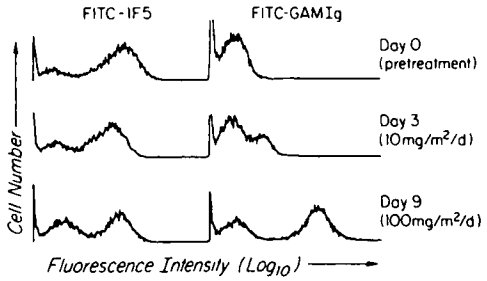

Fig 4. Penetration of MoAb 1F5 into bone marrow of patient 3 during serotherapy as assessed by flow cytometry of mononuclear cells from BM aspirates using FITC-GAMIg (to detect cell-bound 1F5) and FITC-1F5 (to detect unbound Bp35 sites).

Regression of marrow lymphoma was not seen in any of these three patients.

The marrow of patient 4 was unusual in that it appeared to contain tumor cells that did not express the Bp 35 antigen. Although marrow aspirates and biopsies contained unequivocal large cell lymphoma, no tumor cells reactive with FITC-1F5 were detected by flow cytometry. In contrast, tumor cells in cervical and inguinal lymph nodes had the same morphology as the cells in the marrow but reacted strongly with antibody 1F5 as assessed by both immunoperoxidase and immunofluorescence techniques (see Table 2). As would be anticipated, infusion of antibody 1F5 had no effect on the antigen-negative tumor cells in the marrow of this patient.

Effects of 1F5 on lymph nodes. Patients 2, 3, and 4 had evaluable adenopathy that was biopsied before treatment and on the last day of antibody infusion. Immunoperoxidase and immunofluorescent analyses showed no penetration of antibody 1F5 into the nodes of patient 2 (who received 105 mg over ten days). There was minor perivascular penetration detectable only by immunoperoxidase methods in patient 3 (1,032 mg over ten days). In contrast, significant coating of tumor cells detectable by both immunoperoxidase and immunofluorescence (Figs 5 and 6) was present in patient 4 (2,380 mg over seven days) with 69% saturation of available binding sites. In vitro studies showed that an ambient 1F5 antibody concentration of 24 μg/mL was necessary to achieve 69% saturation of cell-surface binding sites. Since the serum 1F5 concentration in patient 4 at the time of his lymph node biopsy was approximately 190 μg/mL, we estimate that a 1F5 antibody gradient of 8:1 existed between serum and lymph node interstitial fluid.

No clinical response was observed in the nodes of patient 2. Some inguinal nodes regressed by 25% in patient 3, but most lymph nodes were unaffected. There was marked regression of all nodes in patient 4 with a calculated >90% reduction in tumor burden (Fig 7). Of note, the diminution of LN size did not begin until day 5 of antibody infusion, and progressive node shrinkage continued for three weeks after cessation of 1F5 infusion. The response duration was brief, however, with regrowth of LN occurring six weeks after therapy.

Overall clinical response. Patient 1 had diminution of

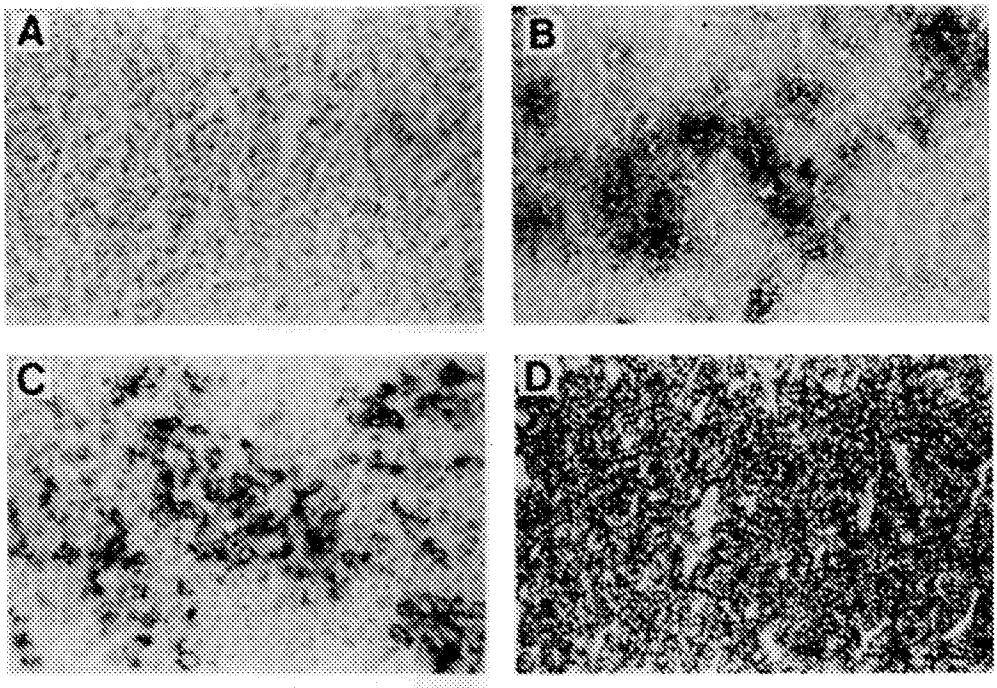

Fig 5. Indirect immunoperoxidase staining of lymph node frozen sections with GAMIg to detect in vivo labeling of tumor cells during murine MoAb 1F5 serotherapy (original magnification × 250). (A) Patient 2: LN biopsy performed on day 10 of therapy while receiving 5 mg/m²/d of antibody 1F5. Negligible staining indicates absence of penetration of LN by antibody at this dose. (B) Patient 3: LN biopsy performed on day 9 of therapy while receiving 100 mg/m²/d of 1F5. Staining of tumor cells in perivascular locations is present. (C) Patient 4: LN biopsy performed on day 10 of therapy while receiving 800 mg/m²/d of 1F5. Peroxidase staining is appreciable at this dose, although the distribution remains heterogeneous. (D) Saturation of 1F5 binding sites in patient 3 by in vitro incubation of an LN section with excess 1F5 antibody. The section shown in this figure was from the same LN biopsy depicted in Fig 4B.

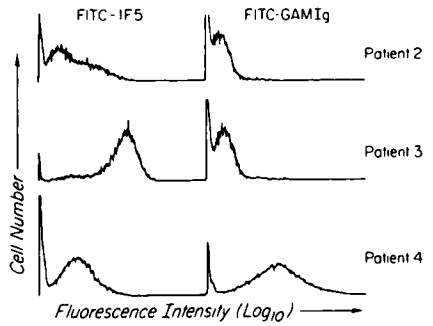

Fig 6. Analysis of 1F5 penetration into LN during serotherapy assessed by flow cytometry of LN suspensions. FITC-GAMIg was used to detect in vivo coating of tumor cells with antibody 1F5. Patient 2 had only a small subpopulation of LN cells possessing the Bp35 antigen (shown with FITC-1F5). No penetration of 1F5 into LN could be shown with FITC-GAMIg. Virtually all LN cells in patient 3 possessed the Bp35 antigen and stained intensely with FITC-1F5, but poor in vivo penetration of 1F5 had occurred as shown by absence of FITC-GAMIg staining. (Immunoperoxidase staining of LN sections was capable of demonstrating some penetration of 1F5 into this LN, however [see Fig 5B]). Patient 4 had significant penetration of 1F5 into LN as shown by staining with FITC-GAMIg.

circulating tumor cells, but progressive liver and marrow lymphoma required premature termination of 1F5 therapy and institution of salvage chemotherapy. Patient 2 had no response of his evaluable marrow or LN disease. Patient 3 had a minor response consisting of transient 90% reduction of circulating tumor cells and 25% shrinkage of some but not all LN but no response in the marrow. Patient 4 had a partial response consisting of 90% reduction of all evaluable LN.

Toxicity. No clinically significant toxicity was observed in any of our patients. Patients 1 and 4 had asymptomatic, intermittent, low-grade fever (38 to 39 °C) lasting six days and two hours, respectively. Transient decrements of platelet and neutrophil counts to 50% to 75% of baseline levels were observed in all four patients. These changes were rapidly reversible in all cases except patient 1, where progressive cytopenias were clearly due to marrow replacement with tumor. In the other three instances, the blood counts stabilized after one to two days and often demonstrated some recovery, even before discontinuation of antibody infusion. No bleeding or infectious episodes occurred during antibody treatment. No allergic, pulmonary, renal, hepatic, or cutaneous sequelae occurred. Renal function as measured by 24-hour creatinine clearance was unchanged after completion of antibody therapy. Complement consumption was observed in patients 1 (40% reduction of CH_{50} and C4 levels) and 3 (97% reduction of CH_{50}, 94% reduction of C4 levels), but circulating immune complexes could not be detected at any time in any patient.

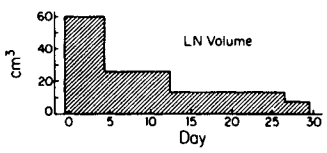

Fig 7. Reduction in tumor burden in patient 4. A 90% reduction in LN volume was observed over a four-week period.

Effects of 1F5 on normal B cells. Attempts to monitor numerical changes and functional alterations of normal B cells in patients receiving 1F5 serotherapy (by assessing proliferative responses to polyclonal B cell mitogens and in vitro Epstein-Barr virus (EBV)-induced immunoglobulin synthesis) were precluded by the extremely low numbers of normal B cells that could be harvested from these patients following antibody infusion. The paucity of B cells was due to two factors: baseline deficiency of normal B lymphocytes (a common feature of advanced, refractory B cell malignancies) and depletion of normal as well as malignant B cells by 1F5 therapy (which has also been documented in normal nonhuman primates infused with anti-CD20 antibodies, [Jeffrey Ledbetter, unpublished results]). Quantitative immunoglobulin levels were carefully monitored in all patients before, during, and for up to five months after 1F5 therapy. Baseline hypogammaglobulinemia was present in patients 1 and 3, but no patient demonstrated a decline in any subclass of immunoglobulin consequent to 1F5 therapy.

Human antimouse antibody levels. IgM HAMA were undetectable by RIA in all patients. Low levels of IgG HAMA (2 × pretreatment control levels) became detectable five months after serotherapy in patient 1 only.

DISCUSSION

This report summarizes our findings in four patients with refractory malignant B cell lymphomas treated with MoAb 1F5 (anti-CD20) by continuous IV infusion for five to ten days. Our study differs from previous serotherapy trials of hematologic malignancies by employing an antibody directed against a nonmodulating antigen. This feature allowed us to maintain continuous high serum antibody levels without inducing the tumor refractoriness generally encountered with modulating antigens.[8-11,20] The continuous infusion mode of administration allowed delivery of very high doses of antibody (up to 800 mg/m^2/d in patient 4) without the significant pulmonary toxicity that is often observed following bolus injection of high MoAb doses.[8,10,21] Serial kinetic measurements revealed a dose-dependent relationship between the amount of antibody infused and the concentration of free MoAb in the blood stream. We found that even low doses of 1F5 (5 to 10 mg/m^2/d) were capable of depleting circulating tumor cells from the blood stream analogous to observations made using murine MoAbs T101 (for chronic lymphocytic leukemia) and J5 (for acute lymphocytic leukemia).[9-11,20] However, in contrast to the studies with modulating antibodies T101 and J5 given by prolonged or repeated administration, the responses induced by the nonmodulating 1F5 were sustained throughout the duration of the infusion (five to ten days).

Although small doses of 1F5 sufficed to deplete circulating tumor cells, penetration of antibody into extravascular sites such as bone marrow and lymph nodes proved to be much more problematic. Intravenous administration of 400 to 800 mg/m^2/d was required to achieve 69% saturation of binding sites on lymph node tumor cells. Even at these doses the intranodal distribution of antibody was heterogeneous. The immunoperoxidase staining patterns observed in LNs

suggested passive diffusion of antibody down a concentration gradient from small blood vessels into the LN parenchyma. The clinical responsiveness observed appeared to correlate with 1F5 dose administered, peak-serum MoAb concentration achieved, and degree of extravascular tissue penetration obtained. A total dose of 52.4 mg was associated with progressive disease (patient 1), 104.8 mg resulted in stable disease in patient 2, 1,032 mg caused a minor response in patient 3, and 2,380 mg produced a partial response in patient 4.

These observations have been made on a very small group of patients, each of whom had a different type of B cell lymphoma. The degree to which our findings might be applicable to other lymphoma patients is unclear, since each patient has a different tumor burden and distribution, different numbers of circulating malignant cells acting to absorb infused MoAb, and different surface densities of the Bp35 antigen. Consequently, the dose levels and kinetic data found in our patients can only serve as a rough guideline for the management of other patients with this antibody. Generalizations from our findings with 1F5 to other MoAbs should be made with caution in light of recent studies demonstrating dramatic, unpredictable kinetic and functional differences among different antibodies recognizing the same antigen.[22]

The toxicity seen in these four patients was insignificant. Minor fever and moderate cytopenias were the only adverse effects observed despite administration of massive doses of antibody 1F5 to patients 3 and 4. Since neither platelets nor neutrophils express the Bp35 antigen or label with FITC-1F5, the exact mechanism for the decrement in neutrophil and platelet counts is uncertain. It is of interest that similar decrements in blood counts have also been observed in patients treated with anti-idiotypic antibodies.[8] Small quantities of antibody might be absorbed via Fc receptors to these cells, which may then be removed from the circulation by the reticuloendothelial system. Although the development of HAMA has been a major problem in some reported series,[8,23] antimouse antibodies were detected in only one of our four patients, and in this patient they did not appear until five months after 1F5 therapy was completed. These findings are in accord with other studies demonstrating that patients with B cell malignancies undergoing monoclonal serotherapy seldom develop HAMA, whereas patients with T cell malignancies or solid tumors receiving similar treatment often develop antimouse antibodies.[24,25]

Previous trials of MoAb serotherapy have also generally encountered minimal toxicity.[3] The major adverse events described to date involved anaphylactoid reactions in patients with large circulating tumor cell burdens and/or high circulating antigen levels given high doses of antibody by rapid bolus injection.[8,10,21] These episodes have been ascribed to pulmonary leukostasis resulting from sequestration of antibody-coated tumor cells in the pulmonary vasculature leading to wheezing, dyspnea, and hypotension. The absence of circulating antigen and the prolonged duration of antibody administration in our trial were mitigating factors that probably helped avoid these untoward sequelae in our patients.

The relative merits of continuous infusion of MoAbs compared with intermittent bolus therapy remain debatable. For many antibodies continuous infusion is not feasible because of antigenic modulation. In such circumstances intermittent therapy is necessary to allow regeneration of cell surface antigen. The bolus method is less cumbersome than continuous infusion and achieves higher peak MoAb concentrations for equivalent doses. Whether the maintenance of uniform high-circulating antibody levels and reduction in toxicity achievable with continuous infusion are sufficiently advantageous to offset the inconveniences remains unanswered. Nevertheless, maintenance of steady state antibody levels in this trial has afforded an advantageous setting for kinetic measurements and for the assessment of the serum concentrations required for MoAb penetration into the extravascular space.

The mechanisms by which unmodified MoAbs might cause elimination of tumor cells in vivo remain controversial. Most workers currently view antibody-dependent cellular cytotoxicity and reticuloendothelial system phagocytosis of MoAb-coated cells as the most likely processes involved.[3,26] Murine MoAbs (including 1F5) fix human complement poorly in vitro, and consequently complement-mediated tumor cell lysis is not thought to be of major significance in vivo. The significant consumption of complement in two of our four patients was unexpected and suggests a possible role for complement in eliminating tumor cells.

The short, incomplete responses obtained with serotherapy using unmodified MoAbs have been of minimal clinical benefit (with the notable exception of the patient described by Miller et al).[7] Consequently, innovative MoAb administration schedules, testing of new antibodies, and administration of antibody conjugates will be necessary if the promise of monoclonal serotherapy is to be realized. Badger et al have already convincingly demonstrated cures of lymphomas in mice treated with radioiodinated MoAbs in a setting in which unmodified MoAbs were ineffective.[27] Recent clinical reports of responses in patients with Hodgkin's disease or hepatoma treated with radioiodinated antiferritin antibodies suggest that this approach will also be useful in man.[28,29] Radiolabeled MoAbs can potentially kill not only the tumor cells to which they bind but could also kill neighboring cells that do not bind antibody by virtue of poor tissue penetration, antigenic modulation, or somatic mutation ("antigen-negative variants"). Toxin-antibody conjugates are similarly promising,[30] although antigens such as CD20, which are not endocytosed after ligand binding,[31] might not be good targets for this approach, since immunotoxin internalization is generally required for cell killing.[32] The findings of our current pilot study should assist in the rational design of subsequent trials employing such radiolabeled or toxin-conjugated immunotoxins.

ACKNOWLEDGMENT

We thank Mary Gallagher, Marsha Bolton, and Terri McLaren for competent assistance in performance of the immunofluorescence and immunoperoxidase studies and Anajane Smith for help in performance of the radioimmunoassays. We are grateful to Drs H. Straley, A. Keller, and S. Speckart for referring patients for these trials.

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Treatment of refractory non-Hodgkin's lymphoma with radiolabeled MB-1 (anti-CD37) antibody.

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The biodistribution, toxicity, and therapeutic potential of anti-CD37 monoclonal antibody (MoAb) MB-1 labeled with iodine 131 (131I) was evaluated in ten patients with advanced-, low- or intermediate-grade non-Hodgkin's lymphomas who failed conventional treatment. Sequential dosimetric studies were performed with escalating amounts of antibody MB-1 (0.5, 2.5, 10 mg/kg) trace-labeled with 5 to 10 mCi 131I. Serial tumor biopsies and gamma camera imaging showed that the 10 mg/kg MoAb dose yielded the best MoAb biodistribution in the ten patients studied. Biodistribution studies in the five patients with splenomegaly and tumor burdens greater than 1 kg indicated that not all tumor sites would receive more radiation than normal organs, and these patients were therefore not treated with high-dose radioimmunotherapy. The other five patients did not have splenomegaly and had tumor burdens less than 0.5 kg; all five patients in this group showed preferential localization and retention of MoAb at tumor sites. Four of these patients have been treated with 131I (232 to 608 mCi) conjugated to anti-CD37 MoAb MB-1, delivering 850 to 4,260 Gy to tumor sites. Each of these four patients attained a complete tumor remission (lasting 4, 6, 11+, and 8+ months). A fifth patient, whose tumor did not express the CD37 antigen, was treated with 131I-labeled anti-CD20 MoAb 1F5 and achieved a partial response. Myelosuppression occurred 3 to 5 weeks after treatment in all cases, but there were no other significant acute toxicities. Normal B cells were transiently depleted from the bloodstream, but immunoglobulin (Ig) levels were not affected, and no serious infections occurred. Two patients required reinfusion of previously stored autologous, purged bone marrow. Two patients developed asymptomatic hypothyroidism 1 year after therapy. The tolerable toxicity and encouraging efficacy warrant further dose escalation in this phase I trial.

PMID: 2666588 [PubMed - indexed for MEDLINE

BLOOD

The Journal of The American Society of Hematology

VOL 68, NO 1 JULY 1986

REVIEW

Immunologic Classification of Leukemia and Lymphoma

By Kenneth A. Foon and Robert F. Todd, III

Important insights into leukocyte differentiation and the cellular origins of leukemia and lymphoma have been gained through the use of monoclonal antibodies that define cell surface antigens and molecular probes that identify immunoglobulin and T cell receptor genes. Results of these studies have been combined with markers such as surface membrane and cytoplasmic immunoglobulin on B lymphocytes, sheep erythrocyte receptors on T lymphocytes, and cytochemical stains. Using all of the above markers, it is now clear that acute lymphoblastic leukemia (ALL) is heterogeneous. Furthermore, monoclonal antibodies that identify B cells, such as the anti-B1 and anti-B4 antibodies in combination with studies of immunoglobulin gene rearrangement, have demonstrated that virtually all cases of non-T-ALL are malignancies of B cell origin. At least six distinct subgroups of non-T-ALL can now be identified. T-ALL is subdivided by the anti-Leu-9, anti-Leu-1, and antibodies that separate T lymphocyte subsets into three primary subgroups. Monoclonal antibodies are also useful in the subclassification of non-Hodgkin's lymphoma, and certain distinct markers can be correlated with morphologic classification. The cellular origin of the malignant Reed-Sternberg cell in Hodgkin's disease remains uncertain. A substantial number of investigators favor a myelocyte/macrophage origin based on cytochemical staining; however, consistent reactivity with antimonocyte reagents has not been demonstrated. Although monoclonal antibodies are useful in distinguishing acute myeloid from acute lymphoid leukemias, they have less certain utility in the subclassification of acute myelogenous leukemia (AML). Attempts to subclassify AML by differentiation-associated antigens rather than by the French-American-British (FAB) classification are underway in order to document the potential prognostic utility of surface markers. Therapeutic trials using monoclonal antibodies in leukemia and lymphoma have been reported. Intravenous (IV) infusion of unlabeled antibodies is the most widely used method; transient responses have been demonstrated. Antibodies conjugated to radionuclides have been quite successful in localizing tumors of <1 cm in some studies. Therapy trials with antibodies conjugated to isotopes, toxins, and drugs are currently planned. Purging of autologous bone marrow with monoclonal antibodies and complement in vitro has been used in ALL and non-Hodgkin's lymphoma; preliminary data suggest that this approach may be an effective therapy and may circumvent many of the obstacles and toxicities associated with in vivo monoclonal antibody infusion.

RECENT ADVANCES in immunology have led to important insights into leukocyte differentiation and the cellular origin of leukemia. It is now possible to define stages of human lymphocyte and granulocyte differentiation precisely using highly specific monoclonal antibodies that define cell surface antigens and molecular probes that identify rearrangement of immunoglobulin and T cell receptor genes. These can be combined with more traditional cell markers such as surface membrane (SmIg) and cytoplasmic immunoglobulin (CIg) on B lymphocytes, sheep erythrocyte receptors on T lymphocytes, and cytochemical stains. In this review, we summarize advances in the classification of leukemia and lymphoma and their importance in our understanding of normal leukocyte differentiation and therapeutic implications.

CELL MARKERS

B lymphocytes. B lymphocytes are usually identified by the presence of SmIg. Progenitors of B lymphocytes, commonly referred to as "pre-B cells," are present in fetal liver and normal bone marrow; the cells display cytoplasmic μ-heavy chain (Cμ) but lack intracytoplasmic light chain and SmIg. B and pre-B lymphocytes may also have receptors for the third component of complement (C'3) and for the Fc portion of IgG. Fc and C'3 receptors are not specific for the B cell lineage and are found in other cells such as monocytes and some nonhematopoietic cells. Similarly, histocompatibility-related antigens (Ia or HLA-DR) are also found on the surface of B cells, but are not unique to them.[1-4] Plasma cells are the most mature B lymphocytes; they lack detectable

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Supported in part by grant no. CA 39064.

Submitted Aug 26, 1985; accepted Feb 1, 1986.

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0006-4971/86/6801-0001$03.00/0

Table 1. Monoclonal Antibodies Reactive with Human B Lymphocytes

Antibody (Subclass)	Pattern of Reactivity	Mol wt of Antigen (kd)	Cluster Designation	Reference
BA-1 (IgM)	B lymphocytes, granulocytes malignant B cells	45,55,65	CD24	4,5
FMC1 (IgM)	B lymphocytes, malignant B cells	NR	NA	6
FMC7	< 50% B lymphocytes, some malignant B cells	NR	NA	7
Anti-B1 (IgG_2)	B lymphocytes, malignant B cells	35	CD20	8
Anti-B2 (IgM)	B lymphocytes, malignant B cells (receptor for Epstein-Barr virus and C3d)	140	CD21	9,10
Anti-B4 (IgG_1)	B lymphocytes, malignant B cells	40	CD19	11
Anti-B5 (IgM)	Activated B lymphocytes, malignant B cells	75	NA	12
P1153/3	B lymphocytes, malignant B cells	NR	NA	13
OKB1 (IgG_1)	B lymphocytes, malignant B cells	168	NA	14,15
OKB2 (IgG_1)	B lymphocytes, granulocytes	NR	NA	14,15
OKB4 (IgM)	B lymphocytes, malignant B cells	87	NA	14,15
OKB7 (IgG_{2a})	B lymphocytes, malignant B cells	175	NA	14,15
Anti-HLB-1 (IgG_{2a})	B lymphocytes, malignant B cells	NR	NA	16
41H.16 (IgG_{2a})	B lymphocytes, malignant B cells	39	NA	17
Anti-BL1 (IgG_1)	Subpopulation of B lymphocytes, malignant B cells, granulocytes	Glycolipid	NA	15
Anti-BL2 (IgG_{2a})	B lymphocytes, malignant B cells, activated T cells	68	NA	15,19
Anti-BL3 (IgG_1)	Subpopulations of B lymphocytes, some malignant B cells, plasma cells, activated T cells	105	NA	15
Anti-PCA-1 (IgG_{2a}) and anti-PCA-2 (IgG_1)	Plasma cells, malignant plasma cells, weakly on monocytes and granulocytes	NR	NA	20
Anti-PC-1 (IgM)	Plasma cells, malignant plasma cells	28	NA	21
LN-1 (IgM)	B lymphocytes, malignant B cells, epithelial tumors	Sialoantigen	NA	22
LN-2 (IgG_1)	B lymphocytes, malignant B cells (nuclear membrane and cytoplasm)	35	NA	22
HD6, HD39, 29-110 SJ10-1H11, SHCL-1	75% of B lymphocytes, most malignant B cells	135	CD22	23
MNM6, PL-13, Blast-2	Germinal center B cells, not on resting B cells, some malignant B cells	45	CD23	23

NR, not reported, NA, not applicable.

The anti-B series, anti PC-1, and anti PCA-1 are available through Coulter Immunology, Hialeah, Fla; BA-1 through Hybritech Inc, San Diego; and the OKB series through Ortho System, Inc, Raritan NJ.

Table 2. Monoclonal Antibodies Reactive with Human T Lymphocytes

Antibody	Pattern of Reactivity	Mol wt of Antigen (kd)	Cluster Designation	Reference
OKT1, anti-T1, anti-Leu-1, 10.2 (Lyt-2), SC-1, A50, T101	Pan-T lymphocyte, pan-thymocyte	65	CD5	26-34
OKT3, anti-T3, anti-Leu-4, UCHT1	Pan-T lymphocyte (mitogenic)	20,20,25	CD3	27,28,35,36
Anti-Ti	Anti-clonotypic (T cell antigen receptor)	49-51 (α) 43 (β)	NA	37-39
12.1, T411	Pan-T, subpopulation of B	120	CD6	40,41
OKT11, anti-T11, anti-Leu-5, 9.6 (Lyt-3)	Pan-T lymphocyte (sheep erythrocyte receptor)	40-50	CD2	42-44
3A1, anti-Leu-9 (4H9), WT1, 4A	Pan-T lymphocyte	40	CD7	45-48
OKT4, anti-T4, anti-Leu-3	T helper/inducer	55	CD4	26-28,49-52
Anti-TQ1	Subset of T inducer cells	NR	NA	53
OKT5, OKT8, anti-T8, anti-Leu-2	T cytotoxic/suppressor	32-43	CD8	26,27,51,52,54,55
OKT6, NA1/34, anti-Leu-6	Thymocytes	45	CD1	27,28,56
OKT9, 5E9	Thymocytes, lymphoblasts, monocytes (anti-transferrin)	90	NA	27,28,57
OKT10	Thymocytes	45	NA	27
Anti-Ta_1	Activated T lymphocytes	105	NA	58
Anti-Tac	Interleukin-2 receptor	55	CD25	59-61

NR, not reported, NA, not applicable.

The OKT series of antibodies is available through Ortho Systems, Inc, Raritan, NJ; Leu series through Becton Dickinson Co, Mountainview, Calif; anti-T through Coulter Immunology, Hialeah, Fla; Lyt through New England Nuclear, Boston; and T101 through Hybritech Inc, San Diego.

SmIg but have CIg. Unlike the CIg found in pre-B lymphocytes, CIg in plasma cells includes both heavy and light chains.

A number of heteroantisera and, more recently, monoclonal anitbodies that identify B cell-associated antigens have been described (Table 1).[4-22] Where applicable, the nomenclature and clusters of differentiation (CD) defined by the Second International Workshop on Human Leukocyte Differentiation Antigens are shown.[23-25]

T lymphocytes. T lymphocytes were initially identified by their ability to bind sheep erythrocytes spontaneously. T lymphocytes also react with T cell-specific antisera and anti-T cell monoclonal antibodies, which may also be used to identify T lymphocytes, and have proven to be more sensitive and discriminatory (Table 2).[26-61] Many of these antibodies react with immature T cells; others react with more mature T cells. Some of these antibodies identify antigens found on all T cells, whereas others occur only on T cell subsets.

Myeloid cells. Monoclonal antibodies to cell suface markers on peripheral blood myeloid cells and their bone marrow progenitors have been extensively investigated.[62-125] Some of these monoclonal antibodies detect antigens expressed by either peripheral blood monocytes or neutrophils. Other reagents identify surface markers common to monocytes and neutrophils; monocytes, neutrophils, and large granular lymphoid cells (LGL); monocytes and platelets; or neutrophils and LGLs (Table 3).

The expression of several monoclonal antibody-defined myeloid antigens corresponds to pathways of normal differentiation within the myeloid lineage. These antibodies are

Table 3. Representative Murine Monoclonal Antibodies That Identify Human Myeloid Cell Surface Antigens: Distribution of Antigen Expression Among Peripheral Blood Cells

Monocytes	Neutrophils	Neutrophils and Monocytes	Neutrophils, Monocytes, and Large Granular Lymphocytes	Monocytes and Platelets	Neutrophils and Large Granular Lymphocytes
Mo2 (CDw14,55)[62-64]*	B40.9[77]	MY7 (CDw13,160)[69]	Mo1 (CD11,155,94)†[62-64]	Mo4 (100)[63]	B73.1 (60-70)‡[112]
Mo3[63]	R1B19 (145,105)[77]	MY8[69]	OKM1 (CD11,155,94)†[106,107]	20.3 (CDw14)[104]	VEP13 (CD16)[113]
UC45 (45)[65]	82H5 (CD15)†[83]	Mo5 (CD11,94)[95]	OKM9 (CD11,155,94)†[108]	OKM5 (88)[108,110]	
UCHM1 (CDw14)[66]	80H.5[84]	B13.4[77,96]	OKM10 (CD11,155,94)†[108]	5F1 (CDw14,85)[98,103]	
UCHALF[66]	TG-1 (CDw15)[85]	B9.8[77,96]	B43.4[77,96]	MPA (135,93)[111]	
S16-144[67,68]	VIM-D5 (CD15,145,105)§[86]	B34.3[77]	αS-HCL 3 or anti-Leu M5(CDw14, 150, 95)[109]	SmO[88]	
MY3 (55)[59]	FMC 10 (CD15)§[87]	AML-2-23[91]			
MY4 (CDw14)[69]	FMC 12 (CD15)§[87]	PM-81[97]			
MY9[70]	FMC 13 (CDw15)[87]	1G10 (CD15)§[98]			
D5D6[71]	AHN-1 (145,105)§[88,89]	M206 (180)[99]			
C10H5[71]	MY-1§[90]	MMA or anti-Leu-M1[100]			
63D3 or antimonocyte .1 (200)[72,73]	PMN6[91]	S4-7 (150)[67,68]			
61D3 or antimonocyte .2 (75)[74]	PMN29[91]	AHN-7‖[101]			
	PMN 7C3¶[92]	80H.1[84]			
	3G8 (60-70)‡[93]	80H.3 (CDw15)[84]			
	1B5[94]				
	4D1 (59)[94]				
MOP-15 (CDw14)[75]		DUHL60.1 (CDw15)[102]			
MOP-9 or anti-Leu-M3 (CDw14)[75]		DUHL60.3 (CDw15)[102]			
Mac-120 or anti-Leu-M2(120)[76]		DUHL60.4 (CDw13)[102]			
		L4F3[103]			
B44.1 (55)[77]		T5A7 (CDw17)[103]			
1D5[78]		20.2 (CDw12)[104]			
PHM3 (50)[79]		VIM-2[105]			
4F2 (40,80)[80,81]					
FMC17 (CDw14)[82]					

*Antibody/antigen (cluster designation [CD], antigen mol wt, kd, reducing conditions), key references (superscript).

†Anti-C3bi receptor antibodies.

‡Anti-Fc receptor antibody.

§Antibodies bind to X-hapten, lacto-*N*-fucose-pentaosyl III.

‖Antibody immunoprecipitates broad band of 28 to 65 kd on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE).

¶Antibody immunoprecipitates two broad bands of 155 to 288 and 75 to 125 kd on SDS-PAGE.

Table 4. Representative Murine Monoclonal Antibodies That Identify Human Myeloid Differentiation Antigens

	S16-114[87,88]	MY9[70,114]	82H5[83]	MY10[115,116]	L1B2[103,117]	R1B19[87,88,77,89]	80H.5[84]	S4-7[87,88]	AHN-7[101]	L4F3[103,117]	T5A7[103,117]	Mo1[85,114,118]	Mo5[85]	MY7[114,118,120]	1G10[88,103,117]	PM81[87,114]	AML-2-23[81,114,121,122]	MY-1[80,118,123]	TG-1[86,85]	PMN 6[81,122]	MY8[85,118,119]	80H.3[84]	B13.4[77,85]	B34.4[77]	Mo2[83,114,124]	MY3/4[114,118,119]	20.3[104]	Mo4[83,124]	5F1[88,103]	SFL 23.6[125]
CFU-GEMM	+	+	+			−		−				−				−	−								−	−			−	−
CFU-GM (d 14)	+	+	+	+	+	−	+	+	+	+	−	−		+	+	+	−	−	−	−	−				−	−			−	−
CFU-GM (d 7)		+			+	+		+		+	+	−		+	+	+	+		−		−				−	−			−	−
Myeloblast	+	+		+	+	+	+	+	+	+	−	−	−	+	+	+	+	+		−	−	−	−	−	−	−	+	−	−	−
Promyelocyte	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−
Myelocyte	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
Metamyelocyte	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−
Neutrophil	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
Monoblast/ promonocyte		+		+	+	−	−		−	+	+	+	+	+	−	+	+		−	−	+	+	+	+	+	+	+	+	+	−
Monocyte	+	+	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	−
BFU-E	+	+	+	+	−	−	−	−		+	−	−		−	−	−	−		−	−	−					−			−	−
CFU-E	−	−			−	−	−	−		−	−	−		−	−				−		−					−			+	+
Erythroid precursor	−	−		−	−	−		−	−	−	−	−	−	−	−	−	−	−	−	−	−		−	−	−		+	−	+	+
Erythrocyte		−	−	−	−	−	−			−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
CFU-Mega			+							+																				
Megakaryocyte			−		−					−	−	−			−						−				−	−	+	+		
Platelet		−	−	−	−	−	−			−	−	−	−	−	−	−	−	−	−	−	−		−	−	−	−	+	+	+	−

therefore useful as tools for identifying hematopoietic cells at various stages of maturation and proliferative potential (Table 4 and Fig 1). Using either complement-dependent monoclonal antibody-mediated lysis (negative selection), or techniques such as fluorescence-activated cell sorting or immune rosetting (positive selection), it is possible to determine patterns of antigen expression by multipotent stem cells (CFU-GEMM) and by stem cells committed to the myeloid (CFU-GM), erythroid (BFU-E, CFU-E), or megakaryocyte/platelet (CFU-Mega) pathways of differentiation. In several reports, myeloid progenitor cells have been purified 50- to 100-fold from bone marrow mononuclear cells[85,126] enabling studies of morphologic and functional characteristics. Certain determinants are uniquely expressed by progenitor cells (eg, MY-10); other antigens are detectable on myeloid, erythroid, or platelet precursors corresponding to morphologically and histochemically distinct stages of maturation within the bone marrow. In the case of neutrophil differentiation, some antigens are either lost (Ia, MY-10) or acquired (Mo1, MY8, 80H.3, or B34.3) as cells progress from myeloblasts to mature neutrophils. Expression of other determinants (82H5, R1B19, S4–7) are maintained on all recognizable myeloid cells.

Although many of these antigenic determinants operationally serve as differentiation markers, some represent epitopes on functionally significant plasma membrane proteins, glycoproteins, and glycolipids. The glycoprotein heterodimer identified by the murine monoclonal antibodies Mo1 and OKM1 is a receptor for the binding of particles opsonized with C3 cleavage product C3bi (CR3 activity).[127,128] Antibodies B73.1 and 3G8 identify an Fc receptor for IgG that is expressed by LGL and/or neutrophils.[93,112] Data from immu-

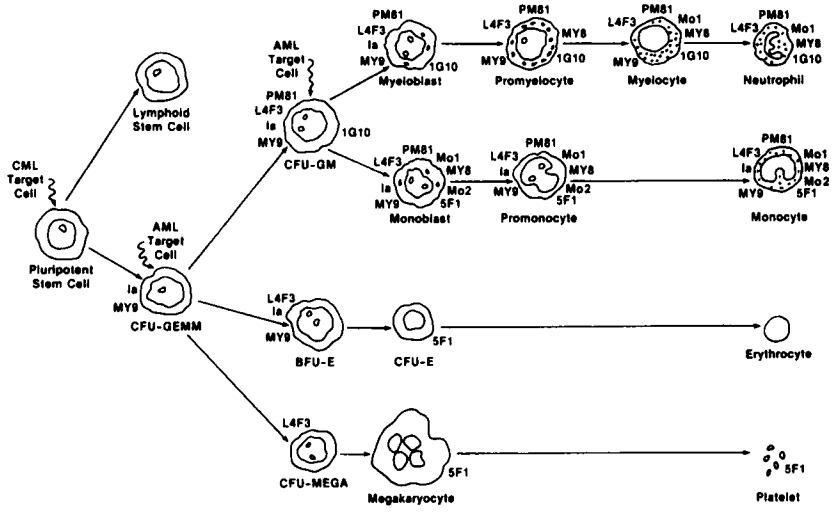

Fig 1. Schematic representation of human myeloid differentiation indicating the cell surface marker phenotype (as defined by selected well-characterized monoclonal reagents) of identifiable maturational steps. Phenotypic expression by monoblasts and promonocytes is tentative and based on positive expression by immature-appearing monocytoid cells in bone marrow. The phenotypes of CFU-GEMM, CFU-GM (early *or* late), BFU-E, CFU-E, and CFU-MEGA are based on the outcome of positive and/or negative selection (antibody-dependent, complement-mediated lysis, immunorosetting, or cell sorting) of human bone marrow cells on subsequent colony growth. Phenotypes of other cells are based on immunofluorescence analyses. Hypothesized sites of CML and AML leukemogenesis are indicated.

Table 5. Monoclonal Antibodies Leukemia-Associated Antigens

Antibody (Subclass)	Pattern of Reactivity	Molecular wt of Antigen (kd)	Cluster Designation	Reference
J5, BA-3, anti-CALLA	Most non-T-ALL, Burkitt's lymphoma, follicular lymphoma, some lymphoblastic lymphoma and T-ALL, rare normal cells	100	CD10	130-136
RFB-1	Myeloid progenitor cells, immature lymphoid bone marrow cells	NR	NA	141
BA-2, SJ-9A4 Du-ALL-1	Lymphohematopoietic bone marrow progenitor cells, most non-T-ALL, platelets	24	CD9	137-140,142
Anti-3-3	T-ALL	35-40	NA	143
Anti-3-40	T-ALL, some non-T-ALL, rare AML vimentin and keratin intermediate filaments in normal cells	35-40	NA	143,144
SN1	T-ALL	NR	NA	145
CALL2	T-ALL	NR	NA	146

NR, not reported; NA, not applicable.

J5 is available through Coulter Immunology, Hialeah, Fla; BA-2 and BA-3 through Hybritech Inc, San Diego.

noprecipitation or immunoblotting analyses indicate that several of these antibodies are specific for epitopes on the same parent structure or even the same epitope.

Leukemia-associated antigens. The common acute lymphoblastic leukemia-associated antigen (CALLA) was originally defined by antiserum produced in rabbits by immunization with SmIg-negative, sheep erythrocyte rosette–negative acute lymphoblastic leukemia (ALL) cells.[129] This antiserum reacted with a 100 kd glycoprotein antigen. Monoclonal antibodies that recognize CALLA (CD10) have recently been described (Table 5).[130,131] Although CALLA is absent on normal peripheral blood lymphocytes, it is not leukemia specific, and is present on normal terminal deoxynucleotidyl transferase (TdT) and Ia antigen–positive bone marrow cells that are thought to be lymphohematopoietic precursor cells.[132] CALLA has also been identified on renal tubular and glomerular cells, mammary epithelium, fetal small intestine epithelial cells,[133] granulocytes,[134] fibroblasts,[134] and melanoma cell lines.[135] CALLA is also present on Burkitt lymphoma cells, follicular lymphoma cells, and cells from 40% of patients with lymphoblastic lymphoma.[136]

P24/BA-2 is a second leukemia-associated antigen with a mol wt of 24 kd defined by the BA-2,[137] SJ-9A4,[138] and DU-ALL-1[139] monoclonal antibodies (CD9). These antibodies do not react with any normal circulating hematopoietic cells except for platelets. They react with most non-T ALL cells and, like CALLA, the P24/BA-2 antigen is present on ~3% to 9% of sheep erythrocyte receptor and SmIg negative TdT positive bone marrow mononuclear cells. This may also represent a bone marrow-derived lymphoid progenitor cell. The anti-J2 antibody[140] has a similar pattern of reactivity as do the BA-2, SJ-9A4, and DU-ALL-1 antibodies. The J2 antigen is also present on activated normal T lymphocytes and may react with the same surface molecule as BA-2. The RFB-1 antibody likewise reacts with immature lymphoid cells in the bone marrow,[141] but differs from BA-2 in its reactivity with myeloid progenitor cells.[141,142] The anti-3-3, anti-3-40,[143,144] SN1,[145] and CALL2[146] antibodies identify antigens found on T-ALL cells but not generally on non-T-ALL or other malignant or normal hematopoietic cells. A summary of the most frequently referenced antibodies and their cluster designations is presented in Table 6.

Immunoglobulin and T cell receptor genes. Recombinant DNA technology has provided important insights into antibody diversity and antigen-specific T cell receptors.[147,148] Immunoglobulins are composed of heavy and kappa and lambda light chains, encoded by genes on chromosomes 14, 2, or 22, respectively.[149-152] Immunoglobulin genes are encoded by discontinuous segments of DNA.[153-158] At one point in development, a potential antibody-producing cell must productively rearrange variable, diversity, and joining genes

Table 6. Frequently Referenced Antibodies with Cluster Designations

Cluster Designation	Antibody
CD1	OKT6, anti-Leu-6, NA1/34
CD2	OKT11, anti-T11, anti-Leu-5, 9.6
CD3	OKT3, anti-T3, anti-Leu-4, UCHT-1
CD4	OKT4, anti-T4, anti-Leu-3
CD5	OKT1, anti-T1, anti-Leu-1, 10.2, T101
CD6	12.1, T411
CD7	anti-Leu-9, 3A1, WT1, 4A
CD8	OKT5, OKT8, anti-T8, anti-Leu-2
CD9	BA-2, SJ-9A4, Du-ALL-1
CD10	J5, BA-3, anti-CALLA
CD11	Mo1/OKM1, Mo5
CDw12	20.2
CDw13	DUHL60.4, MY7
CDw14	Mo2, MY4, MOP-15, FMC 17
CD15	FMC10, VIM-D5, DUHL60.1
CD16	VEP13
CDw17	T5A7
CD19	anti-B4
CD20	anti-B1
CD21	anti-B2
CD22	SHCL-1, HD6, HD39, 29-110
CD23	PL13, MNM6, Blast-2
CD24	BA-1
CD25	anti-Tac

(VDJ), which are then linked to the constant region locus. Immunoglobulin gene rearrangements are hierarchical; μ heavy chain rearrangements precede light chain rearrangements, and κ light chain rearrangement precedes λ light chain rearrangements.[156-158] These rearrangements can be detected by Southern blot analyses of DNA from B cells using appropriately radiolabeled heavy or light chain probes. Heavy chain rearrangements have been identified in non-B cells, but light chain rearrangements appear to be restricted to B cells.[157,159,160] Clonal rearrangements of light chain genes are therefore an extremely sensitive tool to identify B cell malignancies.

The antigen-specific T cell receptor is a heterodimer formed by a 40- to 50-kd α subunit (Tα), and a 40- to 45-kd β subunit (Tβ).[161] It is associated with three 20- to 25-kd peptide chains identified by the T3 monoclonal antibody.[161] Recently, cDNA clones to the Tβ and Tα receptors have been isolated.[162-166] The human Tβ receptor gene has been localized to chromosome 7[167] and the human Tα receptor gene maps to chromosome 14.[168] The less well-defined Tγ receptor gene is currently under investigation. The T cell receptor genes undergo rearrangements in a fashion analogous to that of immunoglobulin genes. The Tγ receptor gene has been shown to be rearranged in murine cytotoxic T lymphocyte cell lines but not myeloma cell lines.[169] Similar to the Tβ chain gene, the Tγ gene rearrangement appears to occur early in T cell development, whereas Tα chain expression occurs later in thymic ontogeny.[170]

T_β gene rearrangements have been detected in malignant human T cells by Southern blotting.[171-173] This technique can detect as few as 1% tumor cells in a mixed cell population[171]; it is a sensitive diagnostic marker for T cell diseases. Rearrangements of the Tβ antigen receptor are reported in 25% of patients with non-T ALL,[174] and in a small proportion of patients with B cell leukemia.[175] This is similar to the rearrangement of immunoglobulin heavy chain genes in 10% of patients with T cell leukemia.[159,160]

Intracellular enzymes and biochemical markers. TdT is present in thymocytes and in a small percentage of bone marrow cells, but not in mature lymphocytes.[176,177] TdT is identified in all subtypes of ALL and is, therefore, not discriminative. TdT has also been demonstrated in a small proportion of acute myelogenous leukemia (AML) cells.[178] Other intracellular enzymes reported useful in identifying subsets of ALL include hexosaminidase, adenosine deaminase,[180] 5'-nucleotidase,[181] purine nucleoside phosphorylase,[182,183] and acid phosphatase.[184] Acid phosphatase is present in T-ALL cells but not in non-T-ALL cells. Cytochemical reactions are useful in the subclassification of AML.[185,186] The M1 through M3 myeloid subtypes contain myeloperoxidase and sometimes nonspecific esterase. Myelomonocytic leukemia cells (M4) also contain myeloperoxidase and nonspecific esterase; the latter is variably inhibited by sodium fluoride. Acute monocytic leukemia (M5) cells contain myeloperoxidase and nonspecific esterase which is completely inhibited by sodium fluoride.

Several surface membrane-associated biochemical markers of leukemia cells have also been described. The glycolipid asialo GM1 is found on cells from patients with ALL (non-T-ALL and T-ALL) but not on cells from patients with other forms of leukemia.[187] Alterations in membrane carbohydrates, such as decreased complex gangliosides,[188] carbohydrate-containing antigens,[189] and receptors for cholera toxin[190] have been reported on leukemia cells.

CLASSIFICATION OF THE LYMPHOID LEUKEMIAS AND LYMPHOMAS

Acute lymphoblastic leukemia. ALL is heterogeneous. The first surface markers used to differentiate subclasses of ALL were receptors for sheep erythrocytes,[191-193] which identify a T cell subset (15% to 20% of cases), and SmIg, which identifies a B cell subset (<5% of cases). Both T and B cell subgroups have an unfavorable prognosis.[194,195] The next important advance in identifying ALL was the development of an antiserum to CALLA.[129] CALLA reactivity identified a non-B, non-T subclass of ALL patients (~70% of cases) with a more favorable prognosis than T-ALL, B-ALL, or non-B, non-T-ALL without CALLA.[195] Other markers such as Ia antigen were commonly found on non-T-ALL and could help differentiate non-T-ALL from T-ALL.[196] By testing for Cμ heavy chain, a subset designated pre-B ALL has been identified.[197-199] Except for the presence of Cμ, this subset expresses the same surface markers as the CALLA form of non-T-ALL; it appears, however, to have a less favorable prognosis.[200]

With the development of monoclonal antibodies, it became evident that the T cell subset of ALL was heterogeneous.[201-205] More recently, studies employing immunoglobulin gene rearrangements and monoclonal antibodies that identify B cell-associated antigens have demostrated that most cases of non-T-ALL are derived from the B cell lineage.[156,206-208] We review these data and present a new classification for ALL based on these recent observations.

Non-T-ALL. Two important areas of research have prompted a reassessment of non-T-ALL. First, monoclonal antibodies that recognize B cell-associated antigens have been identified; many are present on non-T-ALL cells. The most specific of these antibodies is probably anti-B4, which react with 95% of cases of non-T-ALL.[11,208] Second, clonal rearrangements of immunoglobulin genes provide strong evidence for the B cell lineage of most cases of non-T-ALL.[156,206,208]

Although Ia antigen is present on most non-T-ALL cells, and CALLA is present in 75% of cases of non-T-ALL, these antigens are also identified on ~10% of cases of T-ALL. Therefore, B cell-associated antigens (Table 1), which are not identified on T-ALL cells, are the most useful in distinguishing non-T-ALL. The B1 and B4 antigens are model antigens for this discussion.

Less than 5% of cases of ALL express SmIg (usually IgM); these cells are typically classified as B-ALL. These cells generally express other B cell antigens, including B1 (CD20), B4 (CD19), and Ia. B-ALL in children is probably a leukemic phase of non-Hodgkin's or Burkitt's lymphoma.[193,194] Another marker that identifies a subset of non-T-ALL is Cμ heavy chain; κ and λ light chains and SmIg are typically absent.[197] These cells are considered pre-B cells. As

indicated, most cases of non-T-ALL cells of B lineage; thus $C\mu$ is useful in determining the level of differentiation. Pre-B cells that synthesize μ heavy chain are more mature than those pre-B cells that do not synthesize μ heavy chain, but are less mature than those with SmIg.

Nadler and co-workers[208] recently classified 138 patients with non-T-ALL. They divided these cases into four major subgroups. The first subgroup was Ia antigen positive, representing 5% of cases. Another subgroup expressed the Ia and B4 antigens, representing 15% of cases. The third subgroup expressed the Ia, B4, and CALLA antigens, comprising one third of the cases. Finally, one half of the cases of non-T-ALL were Ia, B4, CALLA, and B1 positive. The fourth group was further subdivided into cases with and without $C\mu$. We propose that cases with $C\mu$ be placed in a separate group (group V). The final and most differentiated group, group VI, represents SmIg-positive B-ALL (Table 7).

Nadler and co-workers[208] also studied immunoglobulin gene rearrangements in cells from patients in groups II, III, and IV. Patients in group II (Ia and B4 positive) demonstrated rearranged heavy chain genes, with germ lines for both κ and λ light chain genes. Based on these data, they hypothesized that the group II phenotype represents the earliest stage in B cell maturation. Patients in group III had rearranged heavy chain genes and most had κ light chain gene recombination, either rearrangement or deletion. Patients in group IV had rearranged heavy chain genes; two of four had deletions of κ.

Virtually all non-T ALL cells have immunoglobulin heavy chain rearrangement; not all of them, however, demonstrate light chain rearrangements. Because heavy chain rearrangements also occur in non-B cells[159,160] immunoglobulin heavy chain rearrangements are insufficient to assign non-T-ALL to the B cell lineage. Nadler and co-workers have proposed that the B4 antigen provides the most important independent parameter with which to identify B cell-derived non-T cell ALL. More recently, up to 25% of non-T ALL have been reported to have rearrangements of the $T\beta$ receptor.[174] This observation emphasizes the necessity of combining DNA genotyping and surface marker analyses for more precise classification of leukemia and lymphoma. The remaining 5% of morphologically and cytochemically defined non-T cell ALLs (group I), which express the Ia but not the B4 antigen, most likely represents the earliest stage of pre-B cell differentiation. This hypothetical scheme of early B cell differentiation is further supported by data demonstrating that all of the proposed ALL subgroups can be identified in normal fetal liver and bone marrow and in normal adult bone marrow.[208]

Table 7. Classification of Non-T-ALL

	Antigens					
Group	Ia	B4	CALLA	B1	Cytoplasmic μ	Surface Membrane Immunoglobulin
I	+	−	−	−	−	−
II	+	+	−	−	−	−
III	+	+	+	−	−	−
IV	+	+	+	+	−	−
V	+	+	+	+	+	−
VI	+	+	+/−	+	−	+

T-ALL. T-ALL represents 15% to 25% of cases of ALL. Clinical features associated with T-ALL include a high blast cell count, predominance of older male patients, and mediastinal masses. T-ALL was originally identified by rosetting with sheep erythrocytes. The most sensitive marker for T-ALL is probably the pan-T 40 kd antigen identified by the anti-Leu-9 antibody (CD7). This antigen is present on most thymocytes and T cells but not on non-T-ALL or B cell lymphomas or leukemias.[45-48] In a study of 23 patients with T-ALL, all cases expressed the Leu-9 antigen.[46] Although it was previously reported that anti-Leu-1 (CD5) is the most sensitive marker for T-ALL,[202,209] three of these 23 patients whose cells were anti-Leu-9 positive were negative with anti-Leu-1.[46] Anti-Leu-9 reacts with a small proportion of cases that appear to be myeloid leukemias.[210] In addition, an unusually high incidence of CALLA, Ia, and BA-2 expression has been reported in adults with T-ALL.[211] Recently, rearrangement of the $T\beta$ receptor gene in cases of T-ALL has been reported.[171-175] Two cases of T-ALL with the phenotype of early thymocytes were reported to have no rearranged $T\beta$ receptor genes, suggesting that $T\beta$ rearrangement may occur later in thymocyte development.[212]

Further subclassification of T-ALL is controversial. Reinherz and colleagues proposed a subclassification for T-ALL according to the level of thymic differentiation.[201] Several elements of their subclassification of T-ALL have been confirmed; others are controversial. The most primitive thymocytes, referred to as early or stage I thymocytes, react with T9 and T10 antibodies and account for ~10% of the thymic cells. In their study, Reinherz and co-workers reported that most T-ALL cells express antigens found on early thymocytes. The next level of thymic differentiation, which includes the majority of thymocytes, is referred to as common or stage II. These cells lose T9, retain T10, and acquire T6 (CD1), T4/Leu-3 (CD4), and T8/Leu-2 (CD8) antigens. Approximately 20% of cases of T-ALL express this phenotype. Mature stage III thymocytes no longer express T6 but segregate into T4/Leu-3 or T8/Leu-2 subsets similar to peripheral blood T lymphocytes. Only rarely did Reinherz and colleagues find T-ALL cells with the phenotype of mature thymocytes or circulating T lymphocytes. In a more recent study, Roper and coworkers[204] confirmed many of the findings reported by Reinherz and colleagues, but reported some major differences. In this study, only one third of the T-ALL patients had the phenotype of early or stage I thymocytes; most had the phenotype of either intermediate or late stage thymocytes.

In Table 8, we summarize these data and propose a scheme for the classification of T-ALL. The common marker for all of the subgroups is Leu-9. Nearly all cells also express Leu-1 and most express T11/Leu-5 (CD2) that identifies the receptor for sheep erythrocytes. Cells in subgroup I also express T9 and/or T10. The pan T antigen, identified by T3/Leu-4 (CD3), represents a mature antigen and is not found on group I cells. The T4/Leu-3 helper-associated antigen, the T8/Leu-2 suppressor-associated antigen, and the T6 antigen are not expressed on group I cells.

The next level of differentiation is group II. T9 is found on some cells;[204] however, the T6 antigen as well as the simulta-

Table 8. Classification of T-ALL

Group	Antigens						
	Leu-9*	Leu-1	T11/Leu-5	T3/Leu-4	T4/Leu-3	T8/Leu-2	T6
I	+	+ (90%)	+ (75%)	−	−	−	−
II	+	+	+	+ (25%)	+ (90%)	+ (90%)	+
III	+	+	+	+	+/−†	+/−†	−

*Found on virtually all T-ALL cells.

†No longer simultaneous expression of T4/Leu-3 and T8/Leu-2 as found in group II.

neous expression of T4/Leu-3 and T8/Leu-2 antigens clearly distinguish group II from group I. Some cells in group II may also express T3/Leu-4. Group III T-ALL cells lose the T6 antigen and segregate into cells that have the phenotype of mature thymocytes and T lymphocytes (T3/Leu-4, T4/Leu-3 or T3/Leu-4, T8/Leu-2).

Although Roper and co-workers[204] searched for clinical correlations among these three groups of T-ALL, they found no unique clinical features among the subgroups and no differences in remission duration or survival. However, the groups were too small for statistically valid conclusions. Presently, we believe it useful to subclassify T-ALL using this system, so that data from a number of institutions can be analyzed for clinical correlations between the subgroups of T-ALL (Table 8).

Non-Hodgkin's lymphoma. The non-Hodgkin's lymphomas are a diverse group of neoplasms whose pathologic classification is controversial. It is even more difficult to correlate pathologic classification with immunologic classification. Several immunologic patterns emerge, however, and we will attempt to place them within the non-Hodgkin's lymphoma working classification[213] as well as the Rappaport classification.[214,215]

Follicular or nodular lymphomas. The follicular or nodular lymphomas most likely represent neoplastic proliferation of lymph node-derived follicular center B lymphocytes. The cell type may be a small cleaved cell (nodular lymphocytic poorly differentiated lymphoma by the Rappaport classification), mixed small cleaved and large cleaved or noncleaved cells (nodular mixed), or predominantly large cell (nodular histiocytic). The first two cell types fall within the working classification as low-grade lymphoma, whereas the latter cell type is classified as an intermediate-grade lymphoma. Although the predominantly small cleaved cell will almost always express high-density monoclonal SmIg, larger cells may be SmIg negative.[216,217] However, the small cleaved and large cells will routinely express Ia, B4, and B1 antigens and will often express the B2 antigen.[217] More than half of these cases will also express CALLA.[217,218] Follicular lymphoma cells may be found in the peripheral blood as a "leukemic" phase of the disease (formerly referred to as lymphosarcoma cell leukemia). These cells can usually be differentiated from chronic lymphocytic leukemia (CLL) cells because they may express CALLA, which is not expressed on CLL cells; they do not express the T1/Leu-1 pan-T antigen found on CLL cells; and they generally will have a low percentage of mouse erythrocyte rosette formation (see below).[219,220]

Malignant lymphoma, small lymphocytic. Malignant lymphoma, small lymphocytic (diffuse lymphocytic well-differentiated lymphoma in the Rappaport classification) is a low-grade malignancy, and some cases may be identical to CLL. Also included within this subclassification are the plasmacytoid lymphocytic subgroups with and without an IgM monoclonal gammopathy; some of these cases are similar to Waldenström's macroglobulinemia (described below). Surface markers on these small lymphocytic cells include low-intensity SmIg, mouse erythrocyte receptors, C'3 and receptors for the Fc portion of IgG, and Ia, B1, B2, B4, BA1, and other B cell antigens. These features are similar to CLL, and the cells also express the T1/Leu-1 pan-T antigen.

Malignant lymphoma, diffuse small cleaved cell and diffuse mixed small and large cell. Malignant lymphoma, diffuse small cleaved cell (diffuse lymphocytic poorly differentiated lymphoma in the Rappaport classification) is an intermediate prognostic group. The cells are B lymphocytes that (similar to follicular lymphoma cells) usually display large amounts of monoclonal SmIg. Unlike follicular lymphoma cells, however, they do not usually express CALLA.[218] Similar to follicular lymphoma cells, they do not express the T1/Leu-1 antigen as do cells from most small lymphocytic lymphomas and CLL. However, all these cell types have in common the expression of Ia, B4, B1, B2, and other B cell antigens.[217]

The diffuse mixed small and large cell (diffuse mixed lymphocytic-histiocytic) lymphomas have not been extensively studied but are most likely predominantly B cell diseases. They are also considered an intermediate-grade prognostic group.

Malignant lymphoma, diffuse large cell and large cell immunoblastic. In the working classification, the diffuse large cell lymphomas are considered within the intermediate prognostic group, whereas large cell immunoblastic lymphoma is a high-grade malignancy. By the Rappaport classification, both of these cell types would be described as histiocytic. This is clearly a misdesignation since 80% to 90% of cases represent clonal expansions of malignant B cells.[217,221] A high percentage of these cells express T9 and T10 antigens.[216] Fifty-seven cases of diffuse large cell lymphoma were recently studied and divided into the following subgroups: (a) B1, B4, and SmIg positive; B2 negative (50%); (b) B1, B4, SmIg, and B2 positive (30%); (c) B1 and B4 positive; SmIg and B2 negative (10%); and (4) B1 and SmIg positive, and B2 negative (10%).[222] These data suggest that most of these lymphomas represent the malignant

counterpart of B cells at the midstage of differentiation. Ten to 20 percent of cases are T cell lineage; 2% are derived from the monocyte-myeloid lineage. Recently, clonal rearrangement of the Tβ receptor has been described in patients with T-derived non-Hodgkin's lymphoma.[172,173]

Malignant lymphoma, lymphoblastic. Malignant lymphoma, lymphoblastic, or lymphoblastic lymphoma, is a high-grade malignancy. The nuclear membrane is characteristically deeply subdivided, exhibiting either a lobulated (convoluted) appearance or a fine linear (nonconvoluted) subdivision in a round nucleus. Lymphoblastic lymphoma represents approximately one-third of the cases of non-Hodgkin's lymphomas in children and 5% of cases in adults. The disease is more prevalent in males; these patients often have a mediastinal mass. In some cases, the disease may evolve into a leukemic phase morphologically indistinguishable from T-ALL. The malignant cells are T cells, form E rosettes, react with T cell antisera,[223–225] and have rearrangements of the Tβ receptor.[226] Studies with monoclonal antibodies have demonstrated marked heterogeneity. Lymphoblastic lymphoma cells differ from T-ALL in that the cells rarely express the surface markers common to immature thymocytes (group I);[227] phenotypes are equally divided between group II and group III T-ALL. In 40% of cases, the cells are reported to express CALLA; CALLA expression is less common in T-ALL (10%).[218]

Malignant lymphoma, small noncleaved cell. Malignant lymphoma, small noncleaved cell includes Burkitt's lymphoma and other lymphomas previously designated undifferentiated non-Burkitt type (high grade). Burkitt cells from peripheral blood and bone marrow are usually classified as L3 by the FAB criteria.[185,186] Most cases of Burkitt's lymphoma from Africa are endemic and are associated with the Epstein-Barr virus (EBV). Most non-African cases (nonendemic) are EBV negative.[228] Chromosomal abnormalities involving chromosome 8 (carrying the oncogene c-*myc*) and either 2, 14, or 22 occur in virtually all cases of endemic and nonendemic Burkitt's lymphoma.[229] These are designated t(2;8), t(8;14) and t(8;22), respectively. Usually the light chain class expressed on these cells is correlated with the translocation, ie, κ in t(2;8) and λ in t(8;22). African Burkitt's lymphoma cells have receptors for C'3 and for the Fc portion of IgG in addition to the EBV receptor. American Burkitt's lymphoma cells do not express these receptors.[228] Phenotyping of cell lines derived from patients with undifferentiated lymphoma of the Burkitt's and non-Burkitt's type have demonstrated heterogeneity.[230] These studies suggest that Burkitt cells follow a divergent pathway of B cell evolution because they are all TdT negative (unlike early B cell non-T-ALL). The most primitive of the Burkitt cell lines are Ia and B1 positive and may or may not express CALLA. Maturation was evident in other Burkitt cell lines by the expression of Cμ, surface membrane IgM, and/or IgM secretion. Some of these Burkitt cell lines also expressed the Tac antigen.

Peripheral T cell lymphoma. Peripheral T cell lymphoma would usually be classified as malignant lymphoma, large cell immunoblastic (high grade) under the working formulation. However, this tumor has unique features and will be described separately. The term "peripheral T cell lymphoma" is used to distinguish it from lymphoblastic lymphoma of presumed thymic origin. Peripheral T cell lymphomas are thought to derive from peripheral T lymphocytes in lymph nodes and other nonlymphoid sites. These lymphomas comprise a broad spectrum of morphologic types of lymphocytes. In all instances, the cells have T cell markers admixed with epithelioid histiocytes, plasma cells, eosinophils, and vascular hypertrophy. Clinically, peripheral T cell lymphoma is characterized by generalized lymphadenopathy, weight loss, and a high incidence of pulmonary involvement.[231] Surface markers are usually but not always characteristic of mature T helper cells,[232] including the T4/Leu-3 helper-associated antigen and the T3/Leu-4, T11/Leu-5, and T1/Leu-1 pan-T antigens. Rearrangement of the Tβ receptor has been reported.[226]

Tγ lymphoproliferative disease. Tγ lymphocytes are a subset of T lymphocytes with receptors for the Fc portion of IgG. A high proportion of normal Tγ lymphocytes are LGL. These cells are thought to be responsible for natural killer (NK) and antibody-dependent cell-mediated cytotoxicity in humans[233] and rodents.[234] A lymphoproliferative disorder made up of predominantly Tγ lymphocytes has been described; we refer to this as chronic Tγ lymphoproliferative disease.[235] Typically, patients are elderly males with increased Tγ lymphocytes infiltrating the bone marrow and spleen.[235,236] Although the disease is not rapidly progressive, neutropenia and recurrent infections are common. Most patients do not require chemotherapy. Variants of this disease, including a more aggressive form, have been described.[237] Clonal chromosomal abnormalities,[238] as well as clonal rearrangement of the Tβ receptor, have been reported.[175,239] Cells from chronic Tγ lymphoproliferative disease usually contain acid phosphatase and β-glucuronidase and express the pan-T antigens T3/Leu-4, T11/Leu-5, the suppressor-associated antigens T8/Leu-2, and the NK-associated antigen Leu-7 (HNK-1). Other monoclonal antibodies that react with LGL[240,241] may also prove to be useful.

Cutaneous T cell lymphoma (mycosis fungoides, Sézary cell leukemia). Skin lesions are the most prominent feature of patients with cutaneous T cell lymphoma.[242] Lesions vary from limited plaques to diffuse generalized plaques, tumors, and generalized erythroderma. Rare patients with limited plaque disease and <50% with generalized plaques and tumors have extracutaneous disease detected by light microscopy evaluation of peripheral blood and lymph nodes. Special studies including cytogenetic analysis and electron microscopy indicate blood involvement in >50% of patients with limited plaque disease and most patients with generalized plaques and skin tumors.[243] Analysis of the Tβ receptor rearrangement will likely reveal a higher proportion of cases with nonmalignant cells in the blood and lymph nodes.

The malignant cells in this disorder are characterized by a cerebriform nucleus. In the skin, the cells are referred to as mycosis fungoides cells and in the peripheral blood as Sézary cells. Sézary and mycosis cells form E rosettes, react with T

antisera and anti-T monoclonal antibodies,[244,245] and have clonal rearrangements of the Tβ receptor.[173,175,226,246] In most cases, the cells express the phenotype associated with normal helper/inducer T lymphocytes (T-1/Leu-1, T3/Leu-4, T4/Leu-3 positive)[247-251] and function as helper T lymphocytes in in vitro assays.[252] The 3A1 antibody (CD7), which reacts with >85% of normal circulating T lymphocytes and with mycosis cells in the skin, does not generally react with Sézary cells in the blood.[253]

Adult T cell leukemia/lymphoma. Adult T cell leukemia/lymphoma is associated with a human retrovirus designated human T cell leukemia/lymphoma virus-1 (HTLV-1).[254,255] Virtually all patients tested have antibodies to HTLV-1.[256] Patients with this disease have been identified primarily in Japan, the United States, and the Caribbean. In the United States, the patients are young (median age 33 years), predominantly black, and born in the southeast.[253] Common clinical features include a rapid onset of symptoms with rapidly progressive cutaneous lesions and hypercalcemia. Skin lesions are variable and include small and large discrete or confluent nodules, or nonspecific plaques, papules, or patches. Patients have increased bony turnover with abnormal bone scans and elevated alkaline phosphatase and may have lytic bone lesions.[257] Lymphocytosis is common, and circulating malignant cells are present in low numbers in most patients. Peripheral lymphadenopathy is common, with retroperitoneal and hilar involvement in approximately 50% of cases. Bone marrow, gastrointestinal, pulmonary, leptomeningeal, and hepatic involvement are somewhat less common (20% to 50%). Response to combination chemotherapy is prompt and often complete, but duration of response is short (median 13 months). Opportunistic infections are extremely common in these patients.

The typical malignant circulating cells have moderately condensed nuclear chromatin, inconspicuous nucleoli, and a markedly irregular nuclear contour in which the nucleus is divided into several lobes.[258] These cells typically express the phenotype of helper/inducer T lymphocytes,[259-261] and the Tac antigen (CD25) that identifies the IL-2 receptor.[262] Variability in the expression of T3, T11, and T12 have been reported.[261] Clonal rearrangements of the Tβ receptor are identified in cells from patients with adult T cell leukemia/lymphoma.[173,175,226,239] The leukemic cells are reported to suppress B cell Ig secretion[263] by a complex mechanism involving induction of suppressor cells following activation of normal suppressor cell precursors.[261]

CLL and prolymphocytic leukemia. CLL is a monoclonal proliferation of SmIg-positive B lymphocytes.[264,265] Clonality of CLL has been demonstrated by expression of a single Ig light chain, either κ or λ, on the cell surface membrane.[266,267] More sophisticated techniques have confirmed clonality by showing unique immunoglobulin idiotype specificities,[268] a single pattern of glucose-6-phosphate dehydrogenase activity,[269,270] clonal chromosome abnormalities,[271] or immunoglobulin gene rearrangement,[157] The malignant B cell involved in CLL is an intermediately differentiated cell. The cell appears frozen in differentiation and does not mature to the final stage of B cell development, the mature plasma cell. However, recent data have demonstrated that in vitro treatment of these cells with phorbol esters or pokeweed mitogen can induce differentiation into mature immunoglobulin-secreting plasma cells.[272] In another study, this immunoglobulin secretion was preceded by a rapid increase in the level of mRNA coding for IgM, a predominantly secretory form of mRNA rather than a membrane form of mRNA.[273] This selection is similar to that seen in plasma cells, and the study clearly demonstrated at the molecular level that CLL cells consistently retain the capacity to differentiate to plasma cells and secrete immunoglobulin. Under certain circumstances, CLL cells stimulated in vitro with phorbol esters differentiate into cells with cytoplasmic protrusions and other characteristics of hairy cell leukemia.[274]

The B lymphocyte characteristic of CLL displays a relatively small amount of SmIg, estimated to be ~9,000 molecules per cell.[275] Relatively weak fluorescence of SmIg has been used to distinguish CLL from the leukemic phase of nodular and diffuse lymphocytic lymphomas and from prolymphocytic leukemia in which the cells generally display considerably more SmIg.[276,277] Immunoglobulin isotype analyses indicate that most CLL display a single heavy chain class; typically, μ or μ and δ. Less commonly, γ, α, or no heavy chain determinant is found. CLL cells display either κ or λ light chains but never both. Some data suggest that heavy chain switching can occur in B-CLL, which may indicate increasing maturity of the malignant cell.[277] Other studies indicate that CLL cells contain only μ or μ and δ and that γ is extrinsic and not synthesized by the leukemic cells.[278] Although there has been controversy as to whether CLL B cells contain CIg, the presence of cytoplasmic heavy chains (μ and δ) has been reported in most patients with CLL; no γ or α chains were detected.[279] B-CLL cells display receptors for mouse erythrocytes, a feature characteristic of immature B lymphocytes.[280] The cells also have the receptor for the Fc portion of IgG and complement with a relative increase of C'3d receptors (CR2) over C'3b receptors (CR1); this is typical of immature B cells.[281] B-CLL cells display several antigens, including Ia and human B cell antigens such as BA1, B1, B2, and B4. One unanticipated finding was that B-CLL cells display a 65-kd glycoprotein antigen previously thought to be restricted to T lymphocytes. This antigen was first recognized by using heteroantisera[282]; later, it was recognized with the T101 and equivalent monoclonal antibodies.[31-33] The precise meaning of this anomalous expression of a T cell antigen is unclear, although a normal B cell counterpart has been reported in human tonsil lymph nodes,[283] and stimulation in vitro of normal B cells with phorbol ester may induce expression of this antigen.[284] Recently, the TQ1 antigen, reported to define the inducer of suppression within the T helper subset, was identified on 60 of 75 B-CLL patients' cells.[285]

Rearrangement of immunoglobulin heavy and light chains has been reported as expected in B-CLL cells; however, rearrangement of the Tβ receptor has also been reported in ~10% of cases of B-CLL.[175] This is analogous to the reported Tβ rearrangement in 25% of non-T (pre-B) ALL, and again emphasizes that immunoglobulin and Tβ receptor rearrangement alone are not adequate to assign lineage.

In 3% to 10% of patients with CLL, the disease may evolve

into a diffuse histiocytic lymphoma (Richter's syndrome). This is associated with loss of the TQ1 antigen.[285] Most data suggest that this evolution involves transformed follicular center B cells rather than histiocytes or macrophages. Some transformations represent evolution of the malignant clone with expression of the same monoclonal immunoglobulin and karyotypic abnormality present in the original CLL clone.[286] In other cases, the lymphoma cells have different markers and immunoglobulin gene rearrangements than those of the original CLL cells; these cases probably represent the concomitant development of a B cell lymphoma or a histiocytic malignancy in patients with CLL.[287,288]

Prolymphocytic leukemia (PL) is related to CLL and is also likely to be derived from cells from the medullary cords of the lymph node. Immunoglobulin gene rearrangements of heavy and light chains have been reported.[289] Patients with PL generally have extremely high blast counts and splenomegaly but lack significant lymphadenopathy. Prolymphoblasts likely are activated cells and appear morphologically immature, with a fine lacy nuclear chromatin and one to two nucleoli; they may contain intracytoplasmic granules. These cells generally have higher density SmIg than do CLL cells; they have Ia and B4 antigens and may form rosettes with mouse erythrocytes.[220] PL cells from 14 consecutive patients reacted with the FMC7 monoclonal antibody that recognizes an antigen found on one half of normal B lymphocytes, whereas cells from only 5 of 20 patients with CLL reacted with this antibody.[7]

Approximately 5% of cases of CLL and PL result in a malignant proliferation of T rather than B cells. These cells react with T antisera and anti-T monoclonal antibodies reflecting the phenotypes of mature T lymphocytes; they lack SmIg and other B cell markers.[290,291] Many of these patients have diffuse organ and skin involvement.[290] T-CLL cells have been reported to have either helper or suppressor surface markers.[202,292,293] One patient's cells rosetted with sheep erythrocytes expressed the Leu-2 (suppressor-associated) antigen and also had SmIg and CIg (IgMλ).[294] Other instances in which the leukemia/lymphoma cells expressed characteristic features of both B and T lymphocytes have also been reported.[295]

Hairy cell leukemia. Hairy cell leukemia (leukemic reticuloendotheliosis) is characterized by invasion of the bone marrow and spleen by morphologically distinct mononuclear cells with "hairy" cytoplasmic projections.[296] These cells usually contain an isoenzyme of acid phosphatase (isoenzyme 5) that is resistant to tartrate; this isoenzyme is not unique to hairy cells. Surface markers of hairy cells are most consistent with a monoclonal proliferation of B lymphocytes.[297-300] SmIg with a single light chain is frequently identified,[299,300] as are B cell-associated antigens including Ia, B1, FMC-1, FMC-7, and sometimes BA-1.[299-301] The PCA-1 antigen (but not the PC-1 antigen) typically on plasma cells is identified on hairy cells; these data suggest that hairy cells may be pre-plasma cells.[302] Perhaps the most convincing evidence for the B cell origin of hairy cells comes from studies of immunoglobulin genes which indicate clonal rearrangement of heavy chain genes and at least one light chain gene.[303,304] Most cases of hairy cell leukemia demonstrate the 53-kd to 57-kd Tac antigen (IL-2 receptor) typically identified on select T cell malignancies and activated T cells.[304] Another antigen with a mol wt of 52 to 67 kd, designated HC-2, appears to be restricted to hairy cell leukemia cells.[305,306] The αS-HCL 1 antibody reacts with normal B lymphocytes and B cell malignancies, including hairy cell leukemia.[109] The αS-HCL 3 reacts with normal monocytes and AML cells but is restricted to hairy cell leukemia among the lymphoid malignancies.[109] Approximately 2% to 3% of normal peripheral blood B lymphocytes express this antigen; these appear to be activated B cells.

Myeloma and related disorders. The malignant B cells of Waldenström's macroglobulinemia, heavy chain disease, and multiple myeloma represent a further step in the maturation of medullary cord B cells.[264] Like CLL cells, cells from patients with Waldenström's macroglobulinemia express SmIg and Ia, B1, and B4 antigens.[11] Unlike CLL cells, however, these cells express the PCA-1 antigen but do not express the B2 antigen nor do they rosette with mouse erythrocytes.[4,220] The plasma cell and its malignant counterpart, the myeloma cell, represent the most differentiated B lymphocytes. These cells synthesize large quantities of immunoglobulin and have CIg, but usually lack SmIg and the Ia, B1, B2, and B4 antigens.[307] Plasma cells and myeloma cells, like other mature B lymphocytes, usually lack CALLA, but a recent study has suggested that rare cases of CALLA-positive myeloma represent an aggressive subtype with a poor prognosis.[308] Plasma cells and myeloma cells stain intensely with the OKT10 monoclonal antibody as well as the anti-PCA-1 and anti-PC-1 antibodies.[309,310]

CORRELATES OF CELLULAR DIFFERENTIATION WITH LYMPHOID MALIGNANCIES

Substantial data suggest that the phenotypes of most leukemia cells are not unique but reflect characteristics of normal cells. None of the surface markers we have reviewed are leukemia specific; all can be identified on normal as well as malignant cells. Most of the monocyte, granulocyte, and lymphocyte antigens are found on mature and immature cells. However, CALLA, BA-2, and RFB-1 are expressed primarily on immature bone marrow cells. This observation is consistent with the phenotypes of leukemic cells, since the CALLA and BA-2 antigens are present on primitive leukemia cells (ALL and lymphoid blast crisis of chronic myelogenous leukemia cells) but only rarely on more mature leukemia or lymphoma cells. Distribution of the reactivity of the monoclonal T antibodies is likewise consistent with this hypothesis. The most primitive thymocyte markers, OKT9 and OKT10, are found on most T-ALL cells, whereas T3/Leu-4, T8/Leu-2, and T4/Leu-3, which are found on mature thymocytes and circulating T lymphocytes, are more often identified on more mature T cell leukemias.

A proposed scheme of normal lymphoid differentiation is presented in Fig 2. This scheme is based on the concept that the phenotype of normal lymphoid cells at each level of differentiation can be detected from the phenotype of its malignant counterpart. Although some malignant cells may have an aberrant phenotype, the data presented suggest that

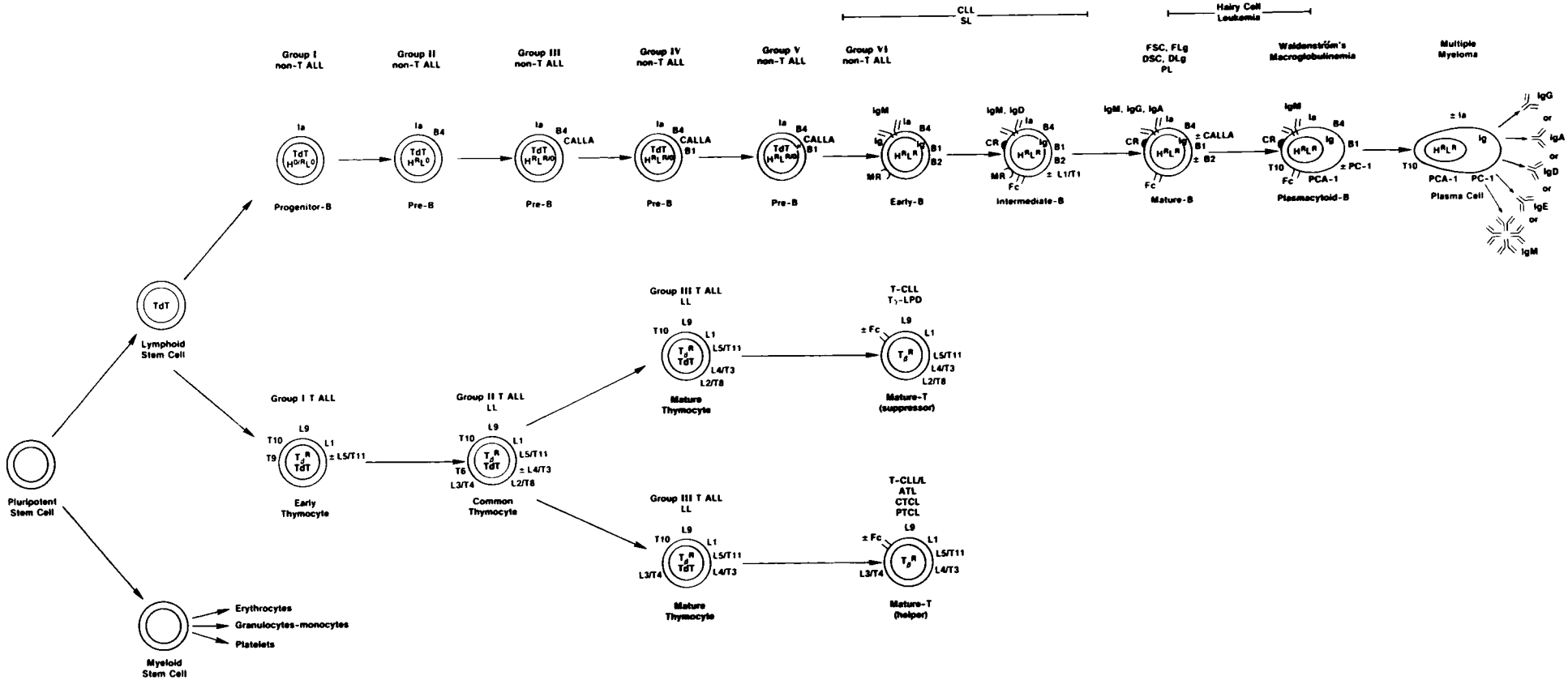

Fig 2. Schematic representation of human lymphoid differentiation and related lymphoid malignancies. ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; SL, malignant lymphoma, small lymphocytic; FSC, malignant lymphoma, follicular small cleaved cell; FLg, malignant lymphoma, follicular large cell; DSC, malignant lymphoma, diffuse small cleaved cell; DLg, malignant lymphoma, diffuse large cell; PL, prolymphocytic leukemia; LL, lymphoblastic lymphoma; Tγ-LPD, Tγ-lymphoproliferative disease; ATL, adult T cell leukemia/lymphoma; CTCL, cutaneous T cell lymphoma; PTCL, peripheral T cell lymphoma; TdT, terminal deoxynucleotidyl transferase; H, heavy chain; L, light chain; O, germline configuration; R, rearranged gene; T^{R}_{β}, clonal rearrangement of the Tβ receptor; MR, mouse rosette; CR, complement receptor.

most malignant lymphoid cells reflect the phenotype of a normal lymphocyte. The proposed phenotype of the progenitor B lymphocyte probably has the same surface markers as the group I non-T-ALL and represents the earliest identifiable B cell. This cell expresses the Ia antigen, but no other B cell-associated antigens. The next level of B cell differentiation coincides with the group II non-T-ALL; heavy but not light chain immunoglobulin genes are rearranged. At the next level of B cell differentiation, the cells express CALLA and light chain gene rearrangements occur; this coincides with group III non-T-ALL. With sequential steps in B cell differentiation, the B1 antigen is expressed, followed by $C\mu$ and then SmIg. At the next level of B cell differentiation, the B cell acquires the B2 antigen and the receptor for mouse erythrocytes; both SmIg and CIg are present. Most CLL cells—and malignant lymphoma, small lymphocytic type cells—express the phenotype of intermediate B lymphocytes. The cells express receptors for complement and the Fc portion of IgG, Leu-1, in addition to the surface markers identified on more primitive B cells. At this level of differentiation, there is low-density SmIg. The maturing B cells express high-density SmIg (IgM, IgG, or IgA) without B2 or mouse erythrocyte receptors. The malignant counterparts of the mature B cell are the follicular small cleaved and large cell lymphomas and the diffuse small cleaved and large cell lymphomas and PL cells. At the next step of maturation, the plasmacytoid B cell secretes Ig, usually of the IgM subclass, and expresses new surface membrane antigens including OKT10, PCA-1, and PC-1. It has recently been demonstrated that hairy cell leukemia falls somewhere between the mature B cell and plasma B cell; they also express the PCA-1 antigen.[302] The plasma cell, the most differentiated B lymphocyte, expresses the same phenotype as myeloma cells. Although these cells have CIg, produce immunoglobulin, and express OKT10, PC-1, and PCA-1, they lose other surface membrane markers, including SmIg, Ia, and B cell antigens.

T cell differentiation follows a distinct pathway. Early thymocytes (stage I) express Leu-9, Leu-1, T9, T10, and often T11/Leu-5 (sheep erythrocyte receptor); this phenotype probably represents the malignant counterpart of group I T-ALL cells. A case has been made that the stage I thymocyte has not yet rearranged the $T\beta$ receptor gene[212]; this remains to be confirmed. The common thymocyte (stage II) no longer expresses T9; it gains T6 antigen and simultaneously expresses the helper-associated (T4/Leu-3) and suppressor-associated antigens (T8/Leu-2). This cell clearly rearranges the $T\beta$ gene, confirming that $T\beta$ rearrangement precedes surface membrane expression of the T3–Ti complex.[212] This cell corresponds to the phenotype of group II T-ALL and some lymphoblastic lymphomas. Subsequently, the cells lose either the helper-associated or suppressor-associated antigens. This is equivalent to group III T-ALL or some cases of lymphoblastic lymphoma. In the final stage of maturation, the suppressor-associated cell (T8/Leu-2) may express the receptor for the Fc portion of IgG as well as the surface markers previously attributed to the mature thymocyte (including the T3–Ti complex), coinciding with the phenotype of some T-CLL cells and chronic $T\gamma$ lymphoproliferative disease. The helper-associated mature T lymphocyte (T4/Leu-3), on the other hand, may express the receptor for the Fc portion of IgM and coincides with the phenotypes of some T-CLL, adult T cell leukemia/lymphoma, cutaneous T cell lymphoma, and peripheral T cell lymphoma.

CLASSIFICATION OF THE NONLYMPHOID LEUKEMIAS AND LYMPHOMAS

Hodgkin's disease. Hodgkin's disease (HD) is a malignant neoplasm of uncertain cellular origin characterized by the appearance of distinctive binucleate or multinucleate giant cells (Reed-Sternberg cells, RSCs) and their mononuclear variants (Hodgkin's cells, HCs).[311] The malignant nature of this disease is suggested by cytogenetic studies that have shown a clonal distribution of chromosomal aneuploidy.[312–314] Considerable debate has arisen as to what constitutes the malignant cell of HD. However, most investigators now agree that the RSCs or HCs (a subset constituting a minute fraction of the tumor mass) represent the neoplastic cell population.[315] The normal cellular counterpart from which RSCs and HCs arise has not yet been identified.[315]

Investigators have used morphology (light and electron microscopy), cell culture, and immunohistochemistry in an attempt to characterize the nature of the RSCs and HCs. Based on these observations, it has been argued that HD arises from the T lymphoid,[316,317] B lymphoid,[318–328] or myeloid-macrophage lineages.[311,329–331] Although this controversy is unresolved, the application of immunologic marker analysis has contributed to our further understanding of the disease, and several general statements can be made. First, with few exceptions, most observers have failed to detect the uniform expression of T cell surface markers (as defined by polyclonal and monoclonal reagents)[328,332–337] by RSCs or HCs, suggesting that these cells are not of T lymphocyte origin. RSCs and HCs have been shown to express the Tac antigen (IL-2 receptor)[338]; in two reports, these cells were found to be T9 positive (transferrin receptor).[332,334] Neither receptor-associated marker is restricted to the T cell lineage.[304,339] Second, although the detection of SmIg or CIg in RSCs and HCs favors a B cell origin,[318,319,322] the expression of these determinants is often polyclonal,[321,340–344] which suggests that immunoglobulin is adsorbed onto RSC and HC cells rather than being synthesized by the malignant cell.[340] There are no convincing data that RSCs or HCs produce immunoglobulin. Immunologic staining of RSCs and HCs for the expression of B cell differentiation antigens has produced conflicting results.[332,333,345] In an interesting case of B cell HD,[346] a patient with nodular sclerosing HD developed a terminal leukemic phase. The circulating HCs expressed the B1 and B4 antigens and had cytoplasmic μ heavy chains and a clonal rearrangement of heavy and light chains (consistent with a B cell origin). Substantial data, however, favor a myeloid-macrophage origin for HD.[340,341,344,347–349] This conclusion is based on the demonstration of nonspecific esterase (NSE) and acid phosphatase, α-1-antitrypsin and α-1-antichymotrypsin, muramidase, lectin-binding properties, and the variable expression of Fc and C3 receptors on

RSC and HC cells. Although short-term cell lines believed to be derived from RSCs demonstrate weak phagocytic activity, and one line was reported to synthesize IL-1,[347,349] other established cell lines have not uniformly shown these activities.[350] In most instances, RSCs and HCs do not react with antibodies to monocytes,[318,332-336,345,350] although in one report a substantial number of biopsy specimens contained RSC and HC positive for markers characteristic of late granulocytic maturation (TU5, TU6, TU9).[333,351] Based on Ia expression[318,332,336,345] and characteristic cytochemical features, other authors have suggested that the cell of origin for HD is a "reticulum cell" (either a dendritic cell or an interdigitating reticulum cell).[336,352] Finally, some data suggest that the RSCs and HCs represent a subset of activated lymphoid cells of either T or B lymphoid origin. This conclusion is based on an immunologic analysis in which RSC and HC uniformly expressed the Ki-1 marker (35 of 35 biopsy specimens of all histological subtypes) as defined by a monoclonal antibody raised by immunization against an established HD cell line.[353] Among normal cells, Ki-1 is expressed by T and B lymphocytes activated in vitro by various stimuli that also induce interleukin-2 (IL-2) receptor expression.[337] In situ staining of biopsy specimens from nonneoplastic and reactive tissues demonstrated Ki-1 expression by a population of normal perifollicular lymphoid cells (lymph node and spleen) and variable degrees of expression by abnormal lymphoid cells in cases of angioimmunoblastic lymphadenopathy and lymphatoid papulosis. Among 290 cases of non-Hodgkin's lymphoma, Ki-1 expression was observed in 19 cases of peripheral T cell lymphoma and in 45 cases of diffuse large cell lymphoma (including 35 specimens expressing T cell surface markers and 7 bearing B cell antigens). These results suggest that Ki-1 is a lymphoid activation antigen that identifies a group of large lymphoid cells in normal and neoplastic tissues (including RSCs) that remains poorly characterized. Another monoclonal reagent, HeFi-1, is similar if not identical to Ki-1.[354]

In summary, the cellular origin for HD remains unclear. Although Ia and T9 antigen staining of RSC and HC cells have been reported, Ki-1 antigen expression may prove to be the most useful immunologic marker for this disease.

RSCs and HCs constitute only a small portion of cells within the tissue of Hodgkin's disease. Recent efforts are directed toward characterizing the remaining cells and have been recently reviewed.[355] Use of in situ techniques has demonstrated that lymphoid tissues involved with HD appear to be heterogeneous in immunohistologic make-up; some cases demonstrate numerous T lymphocytes with few B cells, whereas others exhibit prominent follicles of polyclonal B lymphocytes and only small numbers of T cells within these follicles. In two studies,[335,355] these B cell-rich cases were of the lymphocyte-predominant type. In specimens containing T lymphocytes, RSCs and HCs tend to appear in areas of heaviest T cell infiltration, suggesting a relationship. Many cells within areas of T cell infiltration are Ia or T10 positive, suggesting that these T lymphocytes are activated. Several investigators have demonstrated that most HD-associated T lymphocytes are of the helper cell subset.[332,335,355-357] Genotyping for immunoglobulin and T cell receptor rearrangements may lead to a better understanding of the cellular origin of this disease.

Malignant disorders of macrophages. Several malignant diseases of macrophages (or histiocytes) have been described.[358,359] The term histiocytic lymphoma, used in the Rappaport classification,[215] encompasses a heterogeneous group of neoplasms of large transformed lymphocytes and, rarely, of macrophages.[360,361]

The malignancies of macrophages (histiocytosis X) are heterogeneous.[362] Clinical presentations include solitary benign eosinophilic granuloma, Hand-Schuller-Christian disease, and histiocytic medullary reticulosis; the latter is a generalized systemic disorder characterized by fever, wasting, hepatosplenomegaly, variable lymphadenopathy, and progressive pancytopena due to diffuse tissue invasion by malignant macrophages.[363] The equivalent disease in children is sometimes referred to as Letterer-Siwe disease. Because of morphologic and ultrastructural similarities between malignant macrophages and epidermal Langerhans cells, it has been proposed that these diseases represent a proliferative disorder of Langerhans cells.[364-366] Both cell types possess receptors for C3 and the Fc portion of IgG[367] and express the T6 and Ia antigens.[368,369] The malignant macrophages also express the OKM1 and other macrophage surface markers.[370] An unexpected and unexplained finding was the presence of the T4 antigen in this disorder.[368]

AML. AML is a clonal malignancy of myeloid progenitor cells resulting in excessive proliferation and accumulation of immature hematopoietic elements. The subtypes of this disease are generally classified according to the morphologic similarity of the leukemic cell population to normal myeloid precursors, eg, acute myeloblastic leukemia, acute promyelocytic leukemia, acute monoblastic leukemia, and acute erythrocytic leukemia.

Monoclonal antibodies have been evaluated for reactivity against AML cells (Tables 9 and 10). In all cases, these antibodies identify determinants expressed by either normal circulating myeloid cells or bone marrow progenitors. None of these reagents recognizes a leukemia-specific determinant and, with few possible exceptions,[371-373] attempts to generate leukemia-specific antisera have been unsuccessful. Studies of the reactivity of antimyeloid cell antibodies for AML cells have raised several issues: (a) whether these reagents are specific in their reactivity for myeloid *v* lymphoid leukemia cells; (b) whether antibody reactivity correlates with classification using the FAB nomenclature; (c) whether surface marker expression by myeloid leukemia cells corresponds to stages of normal myeloid differentiation and, if so, whether this is of prognostic significance; (d) whether myeloid leukemia cells in a patient are homogeneous in their expression of surface markers; (e) whether leukemia progenitor cells defined by their ability to form leukemic colonies in vitro exhibit the same antigenic phenotype as their progeny in bone marrow and blood; and (f) whether monoclonal antibodies that identify antigens expressed by myeloid leukemia cells can be used for immunotherapy.

AML v the lymphoid leukemias. Because of differences in prognosis and therapy, it is important to distinguish between AML and the lymphoid leukemias. Although differ-

Table 9. Use of Myeloid Surface Markers to Discriminate Between Acute Myeloid and Lymphoid Leukemia

Monoclonal Antibody	Myeloid Leukemia			Lymphoid Leukemia			References
	AML	CML (MBC)	Total Myeloid	ALL	CML (LBC)	Total Lymphoid	
Mo1/OKM1	63 (228)*	57 (23)	62 (251)	0 (82)	0 (11)	0 (92)	66,106,118,124,389,419
MY7	76 (97)	92 (13)	78 (110)	1 (109)	0 (13)	1 (122)	118,119,419
MY8	53 (73)	7 (15)	45 (88)	0 (82)	0 (11)	0 (83)	118,119,419
MY9	85 (97)	92 (13)	85 (110)	2 (109)	0 (13)	2 (122)	70
VIM-2	91 (66)	93 (30)	92 (96)	5 (60)	0 (11)	4 (71)	106
VIM-D5	68 (116)	88 (8)	69 (174)	2 (88)	NR	2(88)	389,418

MBC, myeloid blast crisis; LBC, lymphoid blast crisis.

*Percentage of patients positive (total number of patients tested). A patient is considered positive for a given marker if >20% of malignant cells bind the monoclonal antibody.

ences in morphology and histochemistry often lead to the correct diagnosis, the distinction between immature variants of AML and ALL is not always evident. Monoclonal reagents that identify antigens expressed by myeloid but not lymphoid leukemias (or vice versa) would therefore be important. Six monoclonal antibodies have been extensively tested for reactivity to myeloid and lymphoid leukemia (Table 9). Each of the six antigenic determinants defined by these antibodies (Mol/OKM1, MY7, MY8, MY9, VIM-2, and VIM-D5) is expressed by more than one half of patients with AML (53% to 91%), defined as antibody binding by >10% to 20% of malignant cells in each patient. The myeloblasts of patients with myeloid blast crisis of CML demonstrate similar frequencies of expression for these determinants except for MY8. Conversely, expression of these antigens on acute lymphoid leukemia cells (including the T and B cell variants of ALL and chronic myelogenous leukemia (CML) lymphoid blast crisis) is rare. Clearly, these monoclonal reagents can complement other tests in the differential diagnosis of AML versus ALL. The accuracy of immunologic diagnosis can be extended by using more than one antimyeloid reagent in conjunction with antibodies that detect antigenic determinants uniquely expressed by B or T lymphoid leukemias (anti-CALLA, B1, B4, OKT3, Leu-4, etc.) (see above). Occasionally, however, this approach has produced seemingly disparate results, with the detection of leukemia cells with myeloid and lymphoid differentiation markers.[374–376] These rare situations may reflect the existence of biopotential clones of malignant cells expressing features of more than one lineage.[377]

Correlation between surface marker phenotype and FAB classification. There are several types of AML differ in morphology, histochemistry, and surface marker expression. Classifications have been proposed to identify these types, based on the hypothesis that this information may be of prognostic and therapeutic significance. The FAB group classification, which relates the morphologic appearance of leukemic cells to presumed normal hematopoietic counterparts, is widely used.[185,186,378,379] Seven subtypes of AML (M1 through M7) are identified: M1 and M2 represent undiffer-

Table 10. Correlation Between Myeloid Surface Marker Expression and FAB Classification System

Monoclonal Antibody		FAB Classification					References
		M1	M2	M3	M4	M5	
VIM-2	(M + N)*	73 (15)†	96 (23)	83 (6)	100 (16)	100 (6)	106
R1B19	(N)	40 (10)	44 (9)	13 (8)	48 (27)	38 (8)	67,68
S4-7	(M + N)	50 (10)	56 (9)	25 (8)	70 (27)	78 (9)	67,68
PM 81	(M + N)	90 (10)	50 (2)		86 (7)	100 (3)	97,122
MY9	(M)	85 (54)‡		100 (6)	81 (31)	83 (6)	70
MY7	(M + N)	78 (54)		67 (6)	81 (31)	50 (6)	118,119
Mo5	(M + N)	50 (38)			74 (27)‡		95
MOP9	(M)	17 (6)	13 (8)	0 (3)	100 (7)	100 (10)	389
AML-2-23	(M + N)	0 (12)	0 (2)		78 (9)	100 (5)	121,122
MY4	(M)	25 (36)		0 (3)	52 (25)	100 (6)	119
UCHM1	(M)	6 (17)			92 (24)	100 (16)	66
MY8	(M + N)	36 (39)		33 (3)	76 (25)	83 (6)	118,119
Mo1/OKM1	(M + N)	39 (124)		100 (3)	91 (101)		66,106,118,124,389
Mo2	(M)	14 (65)			45 (31)		124
VIM-D5	(N)	29 (38)	71 (52)	67 (12)	88 (40)	92 (24)	389,418
82H5	(N)	0 (5)	69 (13)	100 (4)	100 (6)	100 (7)	83

*Antigen expression by peripheral blood monocytes (M) or neutrophils (N).

†Percentage of patients positive (total number of patients tested).

‡Patients with M1 and M2 or M4 and M5 leukemia combined.

entiated and differentiated myeloblastic leukemia; M3, promyelocytic leukemia; M4 and M5, myelomonocytic and monocytic variants; M6, erythroleukemia; and M7, megakaryocytic leukemia. Although some investigators have reported briefer remissions or lower response and survival rates in patients with the M5 variant,[380-382] fewer remissions in erythroleukemia (M6),[380] or longer remissions in promyelocytic leukemia (M3),[380-382] these observations are controversial.[186,381-383] With the development of immunologic reagents that detect antigenic markers expressed by normal and leukemic myeloid cells, analyses have been undertaken to compare the FAB system with patterns of surface marker expression. Table 10 indicates 16 monoclonal reagents whose relative reactivity against FAB-classified AML variants can be critically assessed. Within the first group of seven antibodies (VIM-2, R1B19, S4-7, PM81, MY9, MY7, and Mo5), no clear distinction exists in antigen expression by cells in each of the five FAB variants (M1-M5; too few patients with the M6 and M7 variants were examined to draw conclusions). The frequency of expression by patients in each subclass is generally 50%. In the second group of seven antibodies (MOP9, AML-2-23, MY4, UCHM1, MY8, Mo1/OKM1, and Mo2), there is a trend toward higher frequency of antigen expression among individuals whose leukemia cells display monocytic differentiation (M4 + M5). In the case of VIM-D5 and 82H5, only undifferentiated M1 cells have a lower frequency of expression. None of these reagents demonstrates preferential binding frequency to M1 and/or M2. One antibody, VIE-64, which binds to glycophorin A, displays relative binding specificity toward M6 variant cells.[384] Monoclonal antibody SFL 23.6 has a well-defined reactivity restricted to the erythroid lineage including erythroleukemia cell lines and should be useful in distinguishing M6.[125] Monoclonal antibodies against platelet glycoproteins Ib, IIb/IIIa, and aIIIaa, for factor VIII-related antigen can be used to identify megakaryoblasts.[378] With these possible exceptions, the degree of correlation between surface marker expression and the criteria for FAB classification is not convincing.[385,386]

Subclassification of AML according to differentiation-associated phenotypes as identified by monoclonal antibodies. Because there is controversy over whether the FAB classification system provides prognostic information, alternative classifications have been proposed. In a surface marker analysis of 70 patients with AML, Griffin and co-workers[119] identified four phenotypes based on patterns of surface antigen expression that correlated with phenotypes displayed by myeloid cells during normal differentiation. Group I AML cells (21% of patients) expressed the antigenic phenotype of the CFU-C–committed myeloid progenitor cell (Ia and MY7-positive); group II cells (26%) displayed the phenotypic characteristic of normal myeloblasts (MY7, Ia, and Mo1/OKM1 and My8-positive); group III cells (8%) had a phenotype featured by normal promyelocytes (MY7 and Mo1/MY8-positive; Ia-negative); and group IV cells (45%) with the phenotype of promonocytes and monocytes (MY4, MY7, MY8/Mo1, and Ia-positive). Within these four differentiation-related groups there was considerable morphologic heterogeneity: although all three of the promyelocytic leukemia (M3) patients were in group III and all six monocytic leukemia (M5) patients were in group IV, the myeloid leukemia (M1 and M2) and myelomonocytic leukemia (M4) patients were dispersed throughout all four groups, with a tendency for myeloid patients to be in groups I, II, and III, and myelomonocytic patients to be in groups II and IV. The preliminary finding of a larger prospective analysis involving over 200 patients demonstrates significant differences among these phenotypic groups with respect to complete response rate and disease-free survival (J.D. Griffin, personal communication). Moreover, expression of certain markers appears to be of independent prognostic significance: AML patients with MY7-positive leukemia exhibit a worse prognosis than do MY7-negative patients; the expression of monocyte antigen MY4 is also predictive of a poor response. Several studies of the biological implications of surface marker phenotype in AML are in progress.

A scheme for myeloid differentiation is shown in Fig 1. In an attempt to account for the FAB M4 leukemic cell (bearing features of both granulocytic and monocytic differentiation), Ball and Fanger[122] have proposed that the normal M4 counterpart is an intermediate bipotential precursor cell capable of differentiating along either the monocytic or granulocytic path of differentiation. They further suggest that the myeloblast (M1 and M2), the progenitor of the M4 cell, is likewise bipotential. Given the ability of the promyelocytic leukemia cell line HL-60 to undergo subsequent differentiation toward mature monocytes or neutrophils depending on the nature of the inducing stimulus,[387,388] it appears that the normal promyelocyte is not irreversibly committed to granulocytic maturation. Although these hypotheses are consistent with some experimental observations, considerable additional data are required.

Heterogeneity of surface marker expression by malignant AML cells. Most studies of AML indicate considerable heterogeneity in leukemic cell surface marker expression between patients as well as within a given individual.[62,67,69,95,114,118,122,386,389] Typically, a patient is classified as positive for the expression of a marker if >10% to 20% of the patient's leukemia cells display the determinant. Although certain antigens tend to be expressed by >50% of the leukemic cells of given individuals, variability is considerable. If surface marker expression correlates with the level of myeloid differentiation, these data suggest that the leukemic population is heterogeneous.

AML likely arises from leukemic myeloid progenitor cells, which in some cases can be grown in vitro in semisolid medium.[390-392] The clonogenic leukemia cells (L-CFC) are, by definition, capable of limited proliferation (with a subset capable of self-renewal), a feature that distinguishes them from most leukemia cells that are terminally differentiated.[392,393] Several groups have recently investigated the surface marker characteristics of L-CFC and compared them with the total leukemia population.[70,114,394,395] The surface-marker phenotype of the total leukemia population, as determined by immunofluorescence analysis, may not predict the phenotype of the L-CFC as measured by inhibition of L-CFC growth after antibody-dependent, complement-mediated lysis. In general, the L-CFC has a pattern of

antigenic expression that is more "immature" than that of the predominant phenotype of the total population. L-CFC have been subclassified using multiple markers whose expression on normal CFU-GEMM (Ia, MY9, S3-13, S8-6), early (day 14) CFU-GM (Ia, MY9, PM-81, S3-13, S8-6, S4-7), and late (day 7) CFU-GM (all of the preceding markers plus AML-2-23 and R1B19) are known. Three phenotypically distinguishable levels of differentiation have been identified.[114,394] The degree of maturity, as based on morphology (FAB classification) and expression of "later stage" antigens (beyond the CFU-GM: Mo1, MY3, Mo2) of the total leukemia population, tends to correlate with the L-CFC maturation level (eg, CFU-GEMM level L-CFC are associated with M1 morphology and lack expression of late antigens), suggesting a limited potential for terminal differentiation[114,395] These data suggest that L-CFC are a distinct subset of clonogenic cells among the total leukemia population; these cells may arise at multiple points along the pathway of early myeloid differentiation.

CML. CML is a myeloproliferative disorder characterized by a consistent chromosomal abnormality, the Philadelphia (Ph^1) chromosome. The Ph^1 chromosome results from a reciprocal translocation between chromosomes 9 and 22 designated t(9;22).[396] This translocation results in the transfer of the c-*abl* oncogene from chromosome 9 to the Ph^1 chromosome and the variable reciprocal translocation of c-*sis* from chromosome 22 to 9.[397] The target for leukemic transformation (Fig 3) appears to be at the level of the pluripotential stem cell, since the Ph^1 chromosome is present in all hematopoietic elements of patients with CML, including B and T cells. [398–404] The clonal origin of CML is further indicated by analysis of patterns of expression of glucose-6-phosphate dehydrogenase (G6PD), and adenylate kinase isoenzyme.[398,402] In the chronic phase of the disease, CML is characterized by an overproduction of relatively mature granulocytes. After a variable period of time, with a median of 3 years, most patients enter an acute phase (blast crisis) in which maturation no longer occurs. The acute phase resembles acute leukemia. Approximately one-third of patients with acute-phase CML demonstrate cells with lymphoid features that include the expression of TdT, CALLA, Ia, B1, rarely Cμ and rearrangements in immunoglobulin heavy and light chain genes.[403,405–411] Rare cases of lymphoid acute phase with T cell markers have also been reported.[412–414] Acute phase CML involving myeloid cells is heterogeneous; typically the cells resemble myeloblasts, but erythroblasts, megakaryoblasts, and monoblasts can also be observed. Distinction between lymphoid and myeloid acute phase is important because patients with lymphoid blast crisis may respond to chemotherapy with vincristine (V) and prednisone (P).[410,415–417] In making this diagnostic distinction, the characteristic expression of several myeloid markers (MY7, MY9, VIM-2, and Mol/OKM1) on myeloid blast crisis cells and their lack of expression by lymphoid blast crisis cells (Table 9) provide information complementary to assays for the detection of CALLA, B1, TdT, and CIg.[38,66,70,105,106,118,119,124,409,418,419]

Surface marker analysis may allow further discrimination among the heterogeneous presentation of CML acute phase.

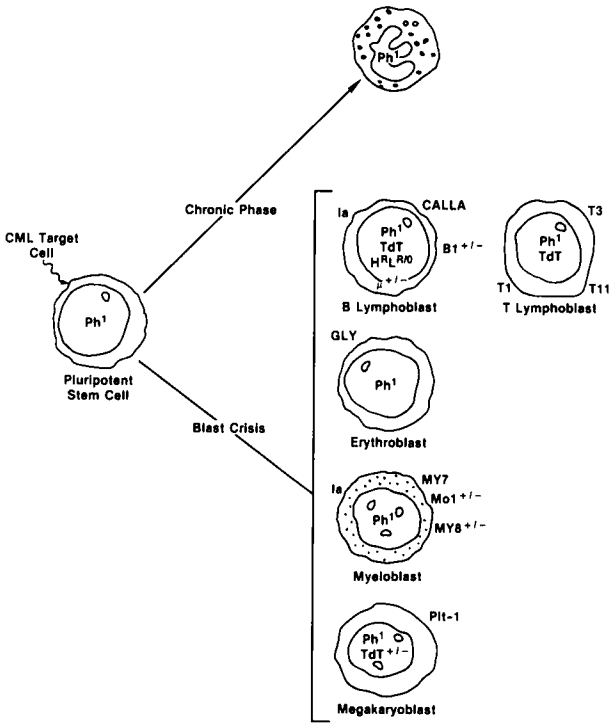

Fig 3. Schematic representation of the origin of chronic and blast crisis phase of chronic myelogenous leukemia (CML) from the target pluripotent stem cell. Phenotypes for various forms of CML blast crisis (based on data of Griffin et al[418]) are indicated. Ph^1, Philadelphia chromosome; TdT, terminal deoxynucleotidyl transferase; GLY, glycophorin A.

Four phenotypes were identified in 30 patients with this disorder based on antigen expression of normal myeloid, erythroid, megakaryocytic, and lymphoid cells.[419] The cells of ten patients exhibited a phenotype corresponding to an immature myeloid cell (Ia, MY7, and Mol-positive); all ten were negative for CALLA, B1, and TdT. These cases were felt to represent "myeloid" blast crisis; none of these patients responded to treatment with V and P. Cells from 11 patients expressed a phenotype similar to acute (early B) lymphoblastic leukemia cells (TdT, Ia, CALLA, and B1-positive; MY7 and Mol-negative); six of nine evaluable patients had a complete response to V and P. Cells from one patient had the phenotype of erythroleukemia (glycophorin A-positive); another patient's cells expressed the phenotype of megakaryocytic leukemia (Plt-1-positive); one patient's cells had features of both myeloid and lymphoid blasts on different cells. Cells from six patients did not express surface markers characteristic of any lineage; these were termed "undifferentiated"; these cases were heterogeneous in expression of TdT; no complete responses to V and P were observed. Thus, in terms of response to V and P therapy, surface marker analysis provided useful prognostic information.

In another series of 45 patients with CML in blast crisis, 28 patients were classified as having "myeloid" blast crisis on the basis of reactivity with at least one of six antimyeloid monoclonal reagents (including VIM-D5 and VIM-2) and no surface expression of T or B cell immune markers or

TdT.[420] Among these myeloid cases, however, only 11 patients expressed granulomonocytic antigens exclusively; the blast cells of 17 patients were additionally positive for platelet/megakaryocyte markers (16 cases) and/or erythroid determinants (three cases). Whether the *same* blast cell co-expressed myeloid, megakaryocytic, or erythroid antigens was not determined. Fourteen patients were classified as having "lymphoid" blast crisis with the phenotypic pattern of CALLA-positive ALL (10 cases), pre-B cell ALL (three cases), or "Null" ALL (one case). Two patients demonstrated a mixed myeloid and lymphoid blast cell phenotype, and a single patient was unclassifiable. Sixteeen of these 45 patients were tested serially during the course of their illness and three demonstrated phenotypic changes. The immunological diagnosis of lymphoid blast crisis was associated with a higher rate of remission than was myeloid blast crisis (57% *v* 4%, respectively) and a longer median survival.

Certain patients with the Ph^1-chromosome are first diagnosed in the acute phase without a preceding history of a chronic phase.[415] Either a chronic phase never existed or it was never detected. Surface-marker analysis may be as useful in the subclassification of these patients' cells as it is in the more typical acute phase that is preceded by a chronic phase.

MONOCLONAL ANTIBODY THERAPY

Several investigators[421-431] have attempted to treat lymphoid or myeloid leukemias with monoclonal antibodies. In some studies, patients with advanced B cell-derived CLL received T101 monoclonal antibody.[421,422] T101 could be safely infused and led to transient reductions in circulating leukemia cells; there was, however, no sustained effect on the bone marrow, involved lymph nodes, or other organs. This therapy resulted in some intravascular cell injury, but destruction in the spleen, liver, and lungs was probably more important. Similar results have been reported in patients with adult T cell leukemia/lymphoma, ALL, and AML treated with other monoclonal antibodies.[423-425] Patients with cutaneous T cell lymphoma who received T101 or anti-Leu-1 have had only transient improvement in skin lesions and lymphadenopathy.[426-429] Side effects of monoclonal antibody therapy are usually minor. Respiratory distress following the rapid infusion of monoclonal antibody has been described,[422] and some patients have demonstrated transient elevation of serum creatinine and hepatic enzymes.[423]

Monoclonal antibody therapy has several shortcomings that must be addressed. First, treatment with antibodies such as T101 results in modulation of the antigen from the cell surface, which prevents antibody binding to the tumor cells. The T101 antigen-antibody complex is pinocytosed into the cytoplasm,[430] a phenomenon that might be advantageous when drugs or toxins are linked to the antibody to enhance its cytotoxicity. Antigen in the circulation poses another potential problem because it might prevent the antibody from reaching the tumor cells. Furthermore, murine antibodies can stimulate production of human anti-mouse antibodies which lead to antibody neutralization. This situation may be correctable by treatment with high initial doses of antibody (> 500 mg) or by simultaneous treatment with immunosuppressive drugs to induce tolerance. In addition, the heterogeneity of antigen expression of tumor cells may necessitate therapy with more than one antibody. Clearly, monoclonal antibody therapy for leukemia and lymphoma is in its earliest stages.

An interesting therapeutic approach with monoclonal antibodies involves the use of anti-idiotype monoclonal antibody reactive with the idiotype of the immunoglobulin on malignant B cells. Such an antibody is by definition specific for a patient's tumor cells. A patient with B cell lymphoma in an accelerated phase who was unresponsive to conventional therapies was treated with an IgG_{2b} anti-idiotype monoclonal antibody.[431] Following eight intravenous (i.v.) infusions, the patient entered a complete remission that has been sustained for >3 years. Results were less impressive in other lymphoma patients treated with this approach with ~50% achieving short-lived partial remissions.[432,433] We developed several monoclonal anti-idiotype antibodies to cells from patients with leukemia and lymphoma.[268] The first patient to undergo treatment had advanced CLL. Sequential anti-idiotype monoclonal antibody therapy with IgG_{2b} and IgG_1 antibody provided no benefit. His therapy was limited because of circulating idiotype immunoglobulin that blocked the binding of the anti-idiotype antibody to the leukemia cells. We were able to reduce the circulating idiotype sufficiently with extensive plasmapheresis.

Although anti-idiotype antibody therapy remains an interesting area of investigation, its applicability is limited by patient specificity (ie, antibodies are "tailor-made" for a single patient) and the presence of antibody in the serum of many patients. Recent data indicate that some tumors are biclonal; this would require the use of more than one antibody.[434,435] In addition, the tumor cell idiotype may be unstable due to somatic mutation within the immunoglobulin variable region genes.[436,437]

A number of centers are studying toxin and drug conjugates with murine antibodies directed toward human tumors; clinical trials have just begun. Antisera and monoclonal antibodies conjugated to radionuclides for tumor imaging have been extensively studied; this subject was recently reviewed.[438] We have used the T101 antibody conjugated to ^{111}indium for imaging in 12 patients with cutaneous T cell lymphoma.[439,440] Tumors as small as 0.5 cm have been localized; however, nonspecific uptake of the immunoconjugate in the liver and spleen has prevented critical evaluation of these organs. This difficulty has been partially circumvented by the administration of intracutaneous injections of the immunoconjugate which cause it to be carried via the lymphatics directly to lymph node sites of disease.[441] This procedure does not, of course, facilitate visualization of extralymphatic disease.

Survival for patients with ALL following relapse has not improved over the past several years with chemotherapy drugs. Allogeneic bone marrow transplantation clearly leads to improved survival, but only 30% to 40% of patients have matched donors.[442-444] An alternative method to allogeneic bone marrow transplantation would make use of monoclonal antibodies to cleanse autologous bone marrow prior to bone marrow transplantation. Patients who are in clinical remis-

sion are likely to have morphologically undetectable tumor cells in their bone marrow; these cells may be identified and destroyed in vitro by specific antibodies and complement or antibodies conjugated to toxins. In one recently reported study, patients with ALL in second or subsequent remission had their bone marrow treated with a mixture of the BA-1, BA-2, and BA-3 monoclonal antibodies and rabbit complement.[445] All the patients were prepared for transplantation with cyclophosphamide and fractionated total body irradiation. Engraftment occurred in all the patients and 7 of the 23 patients were relapse-free from 6 to 32 months (median 21 months) posttransplantation. All but one of the deaths was caused by recurrent leukemia. The researchers concluded that autologous bone marrow transplantation using in vitro-treated marrow was safe, allowed engraftment, and resulted in prolonged survival in some patients with ALL in second or subsequent remission. Similar results have been reported for ALL patients treated with the J5 monoclonal antibody and complement.[446] Relapse of leukemia in these patients may result from the inadequacy of the preparative regimen used to treat the patients prior to transplantation, inadequate removal by the in vitro treatment with monoclonal antibody and complement, or possibly to the lack of the putative graft *v* leukemia effect described in allogeneic bone marrow transplantation.[447] Even in allogeneic transplantation, in which the preparative regimens are identical to those of autologous transplantation, >50% of the ALL patients relapse, suggesting that an insufficient preparative regimen may be the factor leading to relapse in autologous transplantation as well.

In another study, patients with advanced B cell non-Hodgkin's lymphoma underwent in vitro bone marrow treatment with the anti-B1 antibody and complement.[448] Ten of 17 patients are disease-free at a median follow-up of 22 months (L.M. Nadler, personal communication). Despite the presence of the B1 antigen on mature B cells, B cells recovered within the first few months after transplantation, suggesting that the normal B cell progenitor does not express the B1 antigen.

Another approach to cleansing bone marrow in vitro is the use of monoclonal antibodies conjugated to toxins. In one study, whole ricin was conjugated to the T101 and 3A1 antibodies.[449] It was demonstrated that 95% of the tumor colonies were killed whereas 96% of bone marrow progenitor cells survived. Similar results were reported for a panel of anti-T cell monoclonal antibodies conjugated to intact ricin.[450] Other investigators reported results of an immunotoxin synthesized with pokeweed antiviral protein and the B43 antibody directed against Burkitt lymphoma cells.[451] Immunotoxins may prove to have advantages over antibody and complement; not all antibodies fix complement, and immunotoxins may have greater cytotoxic capability.

The use of monoclonal antibodies and antibody immunoconjugates in the treatment and radioimaging of cancer is in its infancy. Although much work must still be done to address the problems of monoclonal antibody therapies, studies in animal tumor models and humans have clearly demonstrated that antibodies alone or antibody conjugates can be safely administered with minimal adverse effects; in selected cases, these may have diagnostic and therapeutic value. Nonspecific localization of antibody in the reticuloendothelial system, host antibody response, and antigenic heterogeneity are major obstacles to safe and effective treatment with monoclonal antibodies. These issues are under investigation in animal models and humans. Although anti-idiotype antibodies are highly specific and have produced excellent responses in a small number of patients, problems such as biclonality of some lymphomas, instability of the idiotype, and the difficulty of tailoring antibodies to individual patients clearly limit the role of anti-idiotype therapy. The utility of purging bone marrow in vitro with antibodies and complement (or antibodies coupled to toxins) is limited to only a few diseases. However, studies have demonstrated that tumor cells can be removed from the bone marrow following in vitro treatment with antibody and complement; treated bone marrow can successfully engraft, and a number of patients have remained disease-free for >2 years. Whether this is related to the in vitro treatment is unknown. This treatment may prove to be an important application of monoclonal antibody therapy, and it bypasses most of the problems associated with in vivo monoclonal antibody serotherapy. Perhaps the most important future role for monoclonal antibody therapy will be in patients with minimal disease in the "adjuvant" setting, in whom antibody conjugates may eliminate micrometastatic deposits of tumor cells. This remains to be addressed in controlled trials.

CONCLUSION

The application of hybridoma technology and the exciting discoveries in molecular biology over the past 10 years have led to major advances in our understanding of the cellular origin of leukemia and lymphoma and will likely lead to a better understanding of the etiology of these diseases. Utilizing these techniques, it is now possible to more accurately diagnose and classify these disorders, sometimes guiding therapeutic decisions. It is also possible to use molecular probes to detect minimal residual disease. In the future, monoclonal antibodies conjugated to isotopes, drugs, and/or toxins will likely have a role in the therapy of certain leukemias and lymphomas. We look forward to this exciting new era in cancer therapy and diagnosis.

ACKNOWLEDGMENT

The authors are grateful to Dr Robert Peter Gale for his critical review of this manuscript, and to Jerrie CeBulky for her skills, patience, and tenacity in typing this manuscript.

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